In the Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-394

ELLIOT L. RICHARDSON, ET AL., PETITIONERS

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 72-414

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, PETITIONER

v.

ELLIOT L. RICHARDSON, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 72-528

CIBA CORPORATION, PETITIONER

v.

ELLIOT L. RICHARDSON, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

No. 72-555

ELLIOT L. RICHARDSON, ET AL., PETITIONERS

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 72-666

USV PHARMACEUTICAL CORPORATION, PETITIONER

v.

ELLIOT L. RICHARDSON, ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

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RELEVANT STATUTES AND REGULATIONS

The Federal Food, Drug and Cosmetic Act, 52 Stat. 1040, as amended by the Harris-Kefauver Act, 76 Stat. 780, 21 U.S.C. 301 *et seq.*:
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In the United States Court of Appeals for the Fourth Circuit

No. 71-1717

HYNSON, WESTCOTT AND DUNNING, PETITIONER

v.

ELLIOT L. RICHARDSON, ET AL., RESPONDENTS

RELEVANT DOCKET ENTRIES

Date	
7/30/71	Petition to set aside order of Commissioner of Food and Drugs filed and cause docketed.
7/30/71	Notification of the filing of the petition, together with a copy of the petition, transmitted to the respondents in Washington, D.C.
8/ 4/71	Appearances (2) for the petitioner filed and entered.
8/ 6/71	Appearance for the petitioner filed and entered.
9/13/71	Certified list of record filed.
10/ 4/71	Appearances (2) for the respondents filed and entered.
10/26/71	Brief for petitioner filed. 25 copies.
10/26/71	Joint appendix filed. 10 copies of volume I and II.
11/19/71	Respondents' request for an extension of time to file their brief filed.
11/19/71	Order extending time to file respondents' brief to December 2, 1971, filed.
12/15/71	Brief for respondent filed. 25 copies.
12/21/71	Reply brief for petitioner filed. 25 copies.
1/13/72	Motion of USV Pharmaceutical Corp. for leave to present oral argument as amicus curiae, filed.
1/14/72	Notice of oral argument mailed to Edward, Williams, Williams, Worley, Patterson, Epstein,

McConachie, Hovendon, McLaren, Hutt, and Pfeifer.

1/19/72 Order granting USV Pharmaceutical Corp. leave to present oral argument as amicus curiae, filed.

1/24/72 Opposition to motion of USV Pharmaceutical Corp. for leave to present oral argument as amicus curiae, filed.

1/24/72 Appearance for amicus curiae filed and entered.

1/25/72 Memorandum for USV Pharmaceutical Corp. in opposition on respondent's motion for reconsideration of order granting leave to argue as amicus curiae, filed.

1/31/72 Order denying government's motion to reconsider, filed.

2/ 2/72 Brief (or memorandum) for amicus curiae filed. 25 copies.

2/ 3/72 Respondent's petition for oral argument to memorandum and argument of amicus curiae, filed.

2/ 7/72 Appearance for the respondents filed and entered.

2/ 7/72 Cause argued before Butzner, Russell and Field, Circuit Judges, and submitted.

2/18/72 Tape mailed to Judge Russell.

5/24/72 Opinion filed.

5/24/72 Opinion and Clerk's Memorandum mailed to counsel of record. (Mailed to Hoffman, Williams, Williams, Worley, McConachie, Epstein, and Hovendon.)

5/24/72 Decree filed. Order of the Commissioner reversed.

6/ 5/72 Petitioner's verified bill of costs, filed.

6/15/72 Certified copy of the decree and printed copy of the opinion transmitted to the Commissioner of Food and Drugs, Dept. of Health, Education and Welfare.

9/13/72 Notice evidencing filing petition for certiorari in the Supreme Court September 11, 1972 filed. (Hynson, Westcott and Dunning, Inc. No. 72–414).

9/13/72 Notice evidencing filing petition for writ of certiorari in the Supreme Court September 11, 1972 filed. (Elliot Richardson—No. 72–394).

10/ 3/72 Certified copies of Volumes I and II of the joint appendix transmitted to the Clerk of the Supreme Court.

1/12/73 Certified copy of order of the Supreme Court granting certiorari January 8, 1973 filed.

2/ 2/73 Certified record in one volume transmitted to the Clerk of the Supreme Court.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
Washington 25, D.C., Dec. 23, 1953.

NDA 8986
HYNSON, WESTCOTT & DUNNING
(Attention: Dr. John H. Brewer)
Charles and Chase Streets,
Baltimore, Maryland.

GENTLEMEN: This will acknowledge your letter of November 4, 1953 and additional information on the manufacturing process personally submitted by Dr. John H. Brewer on November 4, 1953 with reference to your new drug application for "Lutrexin". The application was filed with the Secretary on November 5, 1953.

We have completed our study of this application and in accordance with the provisions of the regulation under section 505(c) of the Act it has become effective.

Our affirmative action in allowing this application to become effective is based on safety alone. All claims are on your own responsibility.

In our opinion the studies submitted with the application were not sufficiently controlled to support the conclusion that "Lutrexin" is an effective treatment for dysmenorrhea, habitual and threatened abortion. We recommend that the article not be marketed for these purposes until adequate evidence is available to demonstrate its value. We believe that it is particularly important not to offer the article at this time for use in habitual and threatened abortion because of the hazards

involved in relying upon a drug the effectiveness of which has not been established.

The label statements "Each tablet contains ——— uterine relaxing factor units" may create the misleading impression that this represents a unit of clinical activity. We suggest that it be revised to read "Each tablet contains ——— guinea pig uterine relaxing factor units". Further, it is recommended that the brochure include the definition of the unit. It is also recommended that the brochure be packaged with the drug. Unless this is done, it is required that the label bear a statement of the usual or recommended dosage in order to comply with the regulation 1.106(b) under section 502(f) of the Act.

Please submit five copies of the final printed label and labeling when available.

Sincerely yours,

(S) Ernest Q. King, M.D.,
ERNEST Q. KING, M.D.,
Acting Medical Director.

Enclosure:
Effective paragraphs.

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE,
FOOD AND DRUG ADMINISTRATION.
Washington 25, D.C., Mar. 23, 1956.

NDA 10144
HYNSON, WESTCOTT AND DUNNING, INC.,
(Attention: Mr. McLaughlin),
Charles and Chase Streets,
Baltimore, Maryland.

GENTLEMEN: This will acknowledge your communications of January 27 and February 29, 1956 submitting additional pertinent information on controls and copies of revised labels pertaining to your new drug application for the preparation "Trexinest". Also acknowledged are communications of November 1, 1955 and February 16, 1956 from The Burrough Bros. Mfg. Co., Baltimore, Md. setting the methods, facilities, and controls they will employ in coating the tablets for you. In addition this will acknowledge a letter dated February 27, 1956 from International Hormones, Inc., Brooklyn, New York, specifying the type conjugated estrogens they will supply to

you and a letter of February 20, 1956 from the Laboratory of Industrial Hygiene, Inc., New York, New York setting forth the procedure they will employ in assaying the tablets for you. The application was filed on March 1, 1956.

Our only comment with respect to the labeling is to suggest the addition of a paragraph containing all the usual estrogen warnings.

We have completed our study of this application and in accordance with the provisions of the regulation under section 505(c) of the Act it has become effective.

Our affirmative action in allowing this application to become effective is based upon considerations of safety alone. Any claims which you make are upon your own responsibility.

Please submit five copies of the final printed label and labeling and three finished market packages of the drug when available.

Sincerely yours,

(S) Barbara Moulton, M.D.,
BARBARA MOULTON, M.D.,
Medical Officer, New Drug Branch, Division of Medicine.

Enclosure:
Effective paragraph.

National Academy of Sciences-National Research Council

(Log 1346)

DIVISION OF MEDICAL SCIENCES

DRUG EFFICACY STUDY

Form A (To be submitted in duplicate by applicant)

1. NDA Number 8986.
2. Date Originally Approved December 23, 1953.
3. Rx ☐ OTC ☐.
4. Brand Name Lutrexin ® Tablets.
5. Applicant's Name Hynson, Westcott & Dunning, Inc.
and Address Charles & Chase Streets, Baltimore, Maryland 21201.

6. Quantitative Formula, Established (Non-Proprietary) Name of Active Ingredients (in order shown on label) Lututrin: Amount (per tablet, per ml., etc.) 3000 units per tablet.

7. Dosage Form (tablets, etc.) Tablets.

8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Oral.

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested. The attached paper by Dr. Rizzolo has been accepted for publication by Clinical Medicine.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white). Our files contain hundreds of testimonial letters from physicians who have used Lutrexin successfully with their families (sample copy attached).

(Blue copy is original—White copy is duplicate—the back of this form may be used if additional space is needed)

Lutrexin Tablets
NDA 8986
LOG 1346

PANEL ON DRUGS USED IN DISTURBANCES OF THE REPRODUCTIVE SYSTEM

INDICATIONS

I. Functional dysmenorrhea

EVALUATION: Possibly effective.

COMMENTS: Because the efficacy of remedies for dysmenorrhea is determined principally by a subjective criterion (i.e., report of relief by the patient), it is the opinion of the Panel that firm reliance can be placed only on data obtained from studies that are well controlled. Although the reports cited below suggest that Lutrexin Tablets may produce varying degrees of relief from dysmenorrhea in some patients, it is the opinion of the Panel that only limited credence can be given to these findings because the designs of the experiments were defective in certain respects. Among the defects noted were failure to use the double-blind technique, inadequate duration of the studies, and populations of subjects too small to be meaningful. The efficacy of Lutrexin Tablets for this indication cannot be determined until the results of well-controlled studies are available for evaluation. This indication should be considered inappropriate if sound documentation is not supplied by the manufacturer.

DOCUMENTATION:

1. Hayden, G. E. Relief of primary dysmenorrhea. Obstet. Gynec. 16:730, 1960.

2. Jones, S. S. Lututrin: a new drug for relief of dysmenorrhea. Northwest Med. 54:1253, 1955.

II. Selected cases of premature labor

EVALUATION: Possibly effective.

COMMENTS: This indication poses several difficulties. The package insert stipulates "selected cases." but offers no criteria

on which the selection is to be made. The manufacturer does not define or describe this indication satisfactorily in the package insert; rather, the reader is referred merely to two clinical reports dealing with "premature labor." In these reports, the authors describe instances where, in their opinion, the threat of premature labor existed. They say that, in many of these cases, they were able to prevent the onset of labor by the administration of Lutrexin Tablets. It is the opinion of the Panel that the diagnosis of premature labor can be made only when labor has clearly started and that one cannot predict which patients will go into premature labor. Therefore, the Panel cannot evaluate the efficacy of Lutrexin Tablets in preventing the onset of premature labor, as one cannot know, with a satisfactory degree of certainty, in which patients premature labor will probably develop. The Panel believes, on the basis of the documentation received and their own experience, that this claim is unwarranted.

DOCUMENTATION: None applicable.

III. Threatened and habitual abortion

EVALUATION: Possibly effective.

COMMENTS: The Panel knows of no satisfactory evidence to support this claim. The claim should be considered inappropriate unless efficacy can be proved by additional documentation provided by the manufacturer.

DOCUMENTATION: None available.

Approved by:

(s) ALBERT SEGALOFF, *Chairman.*

National Academy of Sciences-National Research Council

[Received Jan. 28, 1970]

DIVISION OF MEDICAL SCIENCES

DRUG EFFICACY STUDY

Form A (To be submitted in duplicate by applicant)

1. NDA Number 10144.
2. Date Originally Approved March 23, 1956.
   Supplement effective March 4, 1959.
3. Rx ☒ OTC ☐

4. Brand Name Trexinest ® Tablets.

5. Applicant's Name Hynson, Westcott & Dunning, Inc. and Address Charles & Chase Streets, Baltimore, Maryland 21201.

6. Quantitative Formula, Established (Non-Proprietary) Name of Active Ingredients (in order shown on label) Sodium Estrone Sulfate, Lututrin. Amount (per tablet, per ml., etc.) 1.0 mg. 500 units.

7. Dosage Form (tablets, etc.) Tablets.

8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Oral.

9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)

11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.

12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).
(Blue copy is original—White copy is duplicate—the back of this form may be used if additional space is needed)

TREXINEST
NDA 10144
LOG 825

PANEL ON DRUGS USED IN DISTURBANCES OF THE REPRODUCTIVE SYSTEM

INDICATIONS

I. Menopausal disorders

EVALUATION: Effective, but * * *.

COMMENTS: The estrogenic component of this preparation is a recognized effective therapy for the menopausal syndrome, but there is no evidence that lututrin adds to the

effectiveness of the combination. This claim should be considered inapplicable unless the company can provide sound documentation that lututrin enhances the effectiveness of estrogen in the menopausal syndrome. The documentation submitted originally was anecdotal.

DOCUMENTATION: Inadequate.

Approved by:

(S) ALBERT SEGALOFF, *Chairman.*

33 F.R. 7701 (May 24, 1968)

Food and Drug Administration

DRUGS FOR HUMAN USE

DRUG EFFICACY STUDY IMPLEMENTATION ANNOUNCEMENT REGARDING LUTUTRIN

The Food and Drug Administration has reviewed and evaluated a report received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on the following preparations:

1. Lututrin tablets: 3,000 units of lututrin per tablet; manufactured by Hynson, Westcott & Dunning, Inc., Baltimore, Md. 21201.

2. Trexinest tablets: 500 units of lututrin and 1.0 milligram of sodium estrone sulfate per tablet; manufactured by Hynson, Westcott & Dunning, Inc., Baltimore, Md. 21201.

The Academy report states that lututrin may possibly be effective; however, the Academy also states the claims made for the drug—treatment of functional dysmenorrhea, selected cases of premature labor, and threatened and habitual abortion—are inappropriate or unwarranted in the absence of sound documentation.

The Food and Drug Administration also concludes that the claims for lututrin are inappropriate and unwarranted in the absence of sound documentation. The holder of the new-drug

applications for the drugs listed above is provided 60 days from the date of publication of this announcement in the FEDERAL REGISTER to submit adequate documentation, not previously submitted, in support of the representations made for the product.

The holder of the new-drug applications for these drugs has been mailed a copy of the NAS–NRC report. Any other manufacturer, packer, or distributor of such drug or any other interested person may obtain a copy of the NAS–NRC report on lututrin by writing to the Food and Drug Administration, Press Relations Office, 200 "C" Street SW., Washington, D.C. 20204.

The Commissioner of Food and Drugs invites the holders of the new-drug applications for lututrin as well as any interested person and all persons who may be adversely affected by this announcement to meet informally with officials of the Administration to discuss any medical matters relating to the conclusions regarding this drug.

Persons desiring to attend such meeting should notify the Special Assistant for Drug Efficacy Study Implementation, Bureau of Medicine, Food and Drug Administration, 200 "C" Street SW., Washington, D.C. 20204, and suitable arrangements will be made.

Any written comments on this announcement may be addressed to the Special Assistant for Drug Efficacy Study Implementation at the address given above. Comments regarding medical matters and conclusions to be discussed at the meeting should be received no later than 20 days before any meeting is held.

This notice is issued pursuant to the authority vested in the Secretary of Health, Education, and Welfare by the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 701(a), 52 Stat. 1050–53, as amended, 1055; 21 U.S.C. 352, 353, 371(a)) and delegated to the Commissioner (21 CFR 2.120).

Dated: May 17, 1968.

JAMES L. GODDARD,
Commissioner of Food and Drugs.

34 F.R. 5556 (March 22, 1969)

Food and Drug Administration

[Docket No. FDC-D-123; NDA No. 8-986 and 10-144]

HYNSON, WESTCOTT & DUNNING, INC., LUTREXIN TABLETS, TREXINEST TABLETS

DRUG EFFICACY STUDY IMPLEMENTATION; NOTICE OF OPPORTUNITY FOR HEARING

In an announcement published in the FEDERAL REGISTER of May 24, 1968 (33 F.R. 7701), the holder of the new-drug applications for drugs containing lututrin and any other interested person were invited to submit adequate documentation, not previously submitted, pertinent to the question of effectiveness for the representations made for lututrin.

The additional information received, considered together with the other information available, does not provide substantial evidence of effectiveness of lututrin for its recommended uses.

Therefore, notice is hereby given to Hynson, Westcott & Dunning, Inc., Charles and Chase Streets, Baltimore, Md. 21201, and to any interested person who may be adversely affected, that the Commissioner of Food and Drugs proposes to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of the following new-drug applications and all amendments and supplements thereto:

1. NDA No. 8-986 for Lutrexin Tablets; 3,000 units of lututrin per tablet.

2. NDA No. 10-144 Trexinest Tablets; 500 units of lututrin and 1.0 milligram of sodium estrone sulfate per tablet.

It is proposed to withdraw approval on the grounds that new information before the Commissioner with respect to such drugs, evaluated together with the evidence available to him when the applications were approved, shows there is a lack of substantial evidence of effectiveness of the drugs in that there is a lack of substantial evidence that lututrin, a component of both drugs, has the effect or contributes to the effect

which the drugs purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the applicant and any interested person who would be adversely affected by an order withdrawing such approvals an opportunity for a hearing at which time such persons may produce evidence and arguments to show why approvals of new-drug application No. 8–986 and No. 10–144 should not be withdrawn. Promulgation of the proposed order will cause any drug for human use containing lututrin to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

Within 30 days from the date of publication of this notice in the FEDERAL REGISTER, such persons are required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Office of the General Counsel, Food, Drug, and Environmental Health Division, Room 5440, 330 Independence Avenue SW., Washington, D.C. 20201, a written appearance electing whether:

1. To avail themselves of the opportunity for a hearing; or

2. Not to avail themselves of the opportunity for a hearing.

If such persons elect not to avail themselves of the opportunity for a hearing, the Commissioner without further notice will enter a final order withdrawing the approval of these new-drug applications. Failure of such persons to file such a written appearance of election within 30 days following the date of publication of this notice in the FEDERAL REGISTER will be construed as an election by such persons not to avail themselves of the opportunity for a hearing.

The hearing contemplated by this notice will be open to the public except that any portion of the hearing that concerns a method or process that the Commissioner finds is entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance.

If such persons elect to avail themselves of the opportunity for a hearing by filing a timely written appearance of election,

a hearing examiner will be named by the Commissioner and he shall issue a written notice of the time and place for the hearing.

This notice is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052, as amended; 21 U.S.C. 355) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: March 17, 1969.

HERBERT L. LEY, Jr.,
Commissioner of Food and Drugs.

Via Registered Mail

April 18, 1969.

Miss BERYL S. MCCULLAR,
Hearing Clerk, Department of Health, Education, and Welfare, Office of the General Counsel, Food, Drug, and Environmental Health Division, Room 5440, 330 Independence Avenue SW., Washington, D.C. 20201.

DEAR MISS MCCULLAR: In the Federal Register of March 22, 1969, notice was given to Hynson, Westcott & Dunning, Incorporated, that the Commissioner of Food and Drugs proposes to issue an order withdrawing approval of the new drug applications for Lutrexin Tablets (NDA No. 8-986) and Trexinest Tablets (NDA No. 10-144) on the grounds stated in the notice. The notice offered to Hynson, Westcott & Dunning, Incorporated, an opportunity for a hearing on the question of whether the new drug applications should be withdrawn.

Hynson, Westcott & Dunning, Incorporated elects to avail itself of the opportunity for a hearing.

It is our position, however, that Lutrexin Tablets and Trexinest Tablets are not new drugs under the Federal Food, Drug, and Cosmetic Act, as amended, and that, without regard to other considerations, the Drug Amendments of 1962 are not applicable to those drugs. We therefore reserve the right to contest the jurisdiction of the Commissioner and the Food and Drug Administration in the administrative proceedings, or in judicial proceedings, or in both.

Very truly yours,

HYNSON, WESTCOTT & DUNNING, INC.,
By: J. H. FITZGERALD DUNNING,
President.

FD/C

In the United States District Court for the District of Maryland

Civil Action No. 21112

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, A MARYLAND CORPORATION, CHARLES & CHASE STREETS, BALTIMORE, MARYLAND 21201, PLAINTIFF

vs.

ROBERT H. FINCH, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, WASHINGTON, D.C. 20201

AND

HERBERT L. LEY, JR., COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, WASHINGTON, D.C. 20201, DEFENDANTS

COMPLAINT FOR DECLARATORY JUDGMENT AND INJUNCTIVE RELIEF

Plaintiff brings this complaint (1) for a declaratory judgment that its products Lutrexin (R) Tablets and Trexinest (R) Tablets (hereinafter "Lutrexin" and "Trexinest") are not "new drugs" within the meaning of the definition of that term in the Federal Food, Drug, and Cosmetic Act, as amended by the Drug Amendments of 1962 and that, even if Lutrexin and Trexinest were "new drugs" within the literal meaning of that definition as so amended, they have been exempted from such amendments by specific provision of law; (2) in the alternative for a declaratory judgment that there is not a lack of substantial evidence, within the meaning of Section 505(e)(3) of the Act, that such drugs will have the effect claimed for them in their labeling; and (3) for injunctive and other relief as hereinafter set forth.

For its complaint in this cause, plaintiff alleges:

A. Defendants have proposed, in a Notice of Opportunity for Hearing, (attached hereto as Exhibit No. 1), to withdraw approval of new drug applications (NDA) for Lutrexin and Trexinest on the ground that there is a lack of substantial evidence of effectiveness of the drugs and have offered plain-

tiff an opportunity for a hearing on the proposal to withdraw such approval. Defendants' proposal followed a Drug Efficacy Implementation Announcement Regarding Lututrin, in which it was stated that a National Academy of Sciences-National Research Council panel had evaluated Lutrexin and Trexinest and found lututrin, an active ingredient of the drugs, to be "possibly effective" but that the claims for lututrin are "inappropriate or unwarranted in the absence of sound documentation" (Exhibit No. 2). This evaluation, and the proposal of the Food and Drug Administration to withdraw approval of the NDAs for Lutrexin and Trexinest were made, despite the fact that new information which had become available since the NDAs were approved together with that available at the times the NDAs were approved, constitutes substantial evidence of the effectiveness of the drugs. There is no question of the safety of Lutrexin or Trexinest.

Plaintiff has elected to avail itself of the opportunity for a hearing, reserving its right to contest the jurisdiction of defendants and the Food and Drug Administration. Its letter electing to avail itself of such opportunity is attached hereto as Exhibit No. 3.

B. Lutrexin and Trexinest were regarded as "new drugs" by the Food and Drug Administration at the time new drug applications for those products were approved in 1953 and 1956, respectively, under the Federal Food, Drug, and Cosmetic Act as then in effect. Plaintiff asserts, however, that, regardless of their former status, those products were no longer "new drugs" under the Federal Food, Drug, and Cosmetic Act prior to its amendment in 1962 since, prior to such amendment, they had become "generally recognized * * * as safe" for their intended uses, and that such products did not become "new drugs" by reason of the 1962 amendments, since they are generally recognized as effective for such uses; that, in any event, the products are exempt from the effectiveness requirements of the 1962 amendments; and that therefore these drugs are not subject to proceedings for withdrawal of the approved new drug applications on the ground of lack of substantial evidence of effectiveness.

C. The legal conclusion has been reached by defendants that Lutrexin and Trexinest are "new drugs" and are not ex-

empt from the Drug Amendments of 1962. It is stated in the Notice of Opportunity for Hearing that, if plaintiff (or any other interested person) fails to avail himself of the opportunity for a hearing "the Commissioner without further notice *will* enter a final order withdrawing approval of these new drug applications." (emphasis supplied). If the products in question were no longer regarded by defendants as "new drugs" or were regarded as not subject to the effectiveness requirements of the 1962 Amendments there would be no basis for the withdrawal proceedings. Moreover, the proposal is to withdraw approval on the ground that "* * * there is a lack of substantial evidence of effectiveness of the drugs * * *" without regard to whether the drugs are "generally recognized" as effective by qualified experts and are therefore not "new drugs" under the statute.

D. The contemplated administrative hearing will not offer an opportunity to plaintiff to contest the jurisdiction of defendants on the ground that Lutrexin and Trexinest are not "new drugs". It would be financially and otherwise unnecessarily burdensome to require plaintiff to prepare for and participate in the administrative hearing offered by defendants before obtaining an authoritative ruling on the question of defendant's jurisdiction. The interviewing and production of witnesses to show why approvals of the new drug applications should not be withdrawn would be futile if, as plaintiff contends, defendants do not have jurisdiction over the drugs in question as "new drugs". Yet, if plaintiff should not avail itself of the opportunity for a hearing an order would be issued by defendants withdrawing approval of such applications, as a result of which plaintiff would be subjected to the threat of criminal prosecution, injunction proceedings, and seizure of the drugs, and the allegation that it was precluded from contesting such proceedings because it had failed to exhaust its administrative remedies.

E. The Commissioner could not afford plaintiff a fair and adequate hearing on the question of withdrawal of the NDAs on the ground of a lack of substantial evidence of effectiveness since he has already concluded and has testified before the Subcommittee on Intergovernmental Relations of the House of Representatives, that there is a lack of such evidence; the number and identity of the members of the NAS–NRC evaluating

panel who concurred in or dissented from its report that the products are possibly effective are unknown to plaintiff; and the Subcommittee on Intergovernmental Relations and its Chairman have improperly and coercively intruded into the adjudicatory process of FDA which has been instituted with respect to Lutrexin and Trexinest. These factors deprive the contemplated hearing of even the appearance of impartiality.

* * * * *

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
Sep. 18, 1969.

J. H. FITZGERALD DUNNING,
President, Hynson, Westcott & Dunning, Inc., Pharmaceutical Laboratory, Baltimore, Maryland 21201.

DEAR MR. DUNNING: This is in further response to your letter of August 18, 1969, requesting information pertaining to the report of the Panel on Drugs Used in Disturbances of the Reproductive System, National Academy of Sciences-National Research Council, on the products Lutrexin Tablets and Trexinest Tablets. Our reply to your specific requests is as follows:

1. Neither the United States Food and Drug Administration, the Consumer Protection and Environmental Health Service, nor the Department of Health, Education, and Welfare has a Curriculum Vitae of the chairman and members of the Panel.

2. A copy of the Panel report on Trexinest Tablets is enclosed.

3. Copies of the contract between the Food and Drug Administration of the National Academy of Sciences-National Research Council, Contract No. FDA 66–197 (NEG), dated April 29, 1966, and Supplemental Agreement No. 1, dated June 17, 1966, are enclosed.

4. No instructions were issued by the Food and Drug Administration or the Department of Health, Education, and Welfare other than the contract itself.

5. The Department of Health, Education, and Welfare and the Food and Drug Administration issued no instructions or guidelines to the Panel on Drugs Used in Disturbances of the Reproductive System, nor did they communicate in any way with the Panel respecting any efficacy study of any product,

including Lutrexin Tablets and Trexinest Tablets. As far as this Department is aware, the only instructions to the Panel are found in the document, Guidelines for the Drug Efficacy Study of the National Academy of Sciences-National Research Council; a copy of those "Guidelines" is enclosed.

6. The Food and Drug Administration, the Consumer Protection and Environmental Health Service, and the Department of Health, Education, and Welfare do not have any report of any deliberations, minutes, notes, or other material of the National Academy of Sciences-National Research Council Panel. The National Academy of Sciences-National Research Council Drug Efficacy Study Group may be able to inform you whether or not such documents exist.

7. Other than the references listed under the heading, Documentation, by the Panel in its reports on Lutrexin and Trexinest, we do not know what medical or scientific literature was relied upon by the Panel.

8. Neither the Food and Drug Administration, the Consumer Protection and Environmental Health Service, nor the Department of Health, Education, and Welfare has any statement, other than the reports themselves, reflecting the view of each member of the Panel concerning the effectiveness of Lutrexin and Trexinest.

9.–11. We have no information concerning whether the Panel solicited opinions from outside consultants, the manner in which the Panel's conclusion was reached, or whether any independent clinical studies of the effectiveness of Lutrexin and Trexinest were made by the Panel or on its behalf.

12. The Food and Drug Administration has not conducted any independent clinical study or other scientific investigation of the effectiveness of Lutrexin and Trexinest at any time.

13. (a) and (b) The information submitted by your firm to the Food and Drug Administration by letters dated July 22, 1968, and November 1968 was not submitted to the Panel, since the Panel had concluded its report and had it submitted to the Food and Drug Administration prior to May 23, 1968, the date and the report was sent to your firm.

(c) Your firm has elected to avail itself of the opportunity for a hearing on the question of withdrawal of approval of the

New Drug Applications for Lutrexin and Trexinest. As you know, there is no provision for prehearing discovery in the rules of practice which govern such hearings. Written reports and memoranda prepared by Food and Drug Administration personnel prior to the issuance of the Federal Register announcement affording your firm an opportunity for a hearing on the withdrawal of the approval of the New Drug Applications for these drugs are internal-working papers which are specifically exempt from disclosure by the Public Information Act, 5 U.S.C. 552(b)(5). The official responsible for the final decision of any Food and Drug Administration action is Dr. Herbert L. Ley, Jr., Commissioner of Food and Drugs.

Sincerely yours,

(S) Morton A. Lebow,
MORTON A. LEBOW,
Acting Associate Director of Information for Public Services.

DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Maryland 20852, May 19, 1970.

NDAs 8-986; 10-144
Certified Mail Return Receipt Requested

HYNSON, WESTCOTT & DUNNING, INC.,
Charles and Chase Streets,
Baltimore, Maryland 21201.

GENTLEMEN: A Notice of Opportunity for Hearing was published in the FEDERAL REGISTER of March 22, 1969 (34 F.R. 5556) announcing that the Commissioner of Food and Drugs proposed to issue an order withdrawing approval of your new-drug applications Nos. 8-986 and 10-144 for Lutrexin Tablets and Trexinest Tablets, respectively. Pursuant to that notice you filed an appearance electing to avail yourself of the opportunity for a hearing on that proposal.

Your attention is invited to the enclosed final order published in the FEDERAL REGISTER of May 8, 1970, promulgating Hearing Regulations and Regulations Describing Scientific

Content of Adequate and Well-Controlled Clinical Investigations. These regulations describe th scientific content of adequate and well-controlled clinical investigations and set forth the procedural requirements for requesting public hearings and demonstrating that there is a genuine and substantial issue of fact that requires a hearing.

The May 8 regulations are applicable to any reqeust for a hearing. You should amend your request for a hearing to comply with those regulations, i.e., by submitting a well-organized and full-factual analysis of the clinical and other investigational data you are prepared to prove in a hearing, setting forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing.

Within 30 days after the date of receipt of this letter such an amendment should be filed with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6–62, 5600 Fishers Lane, Rockville, Maryland 20852.

Sincerely yours,

(S) Charles C. Edwards,
CHARLES C. EDWARDS, M.D.,
Commissioner of Food and Drugs.

Enclosures.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED,
Baltimore 1, Md., June 1, 1970.

Office of J.H.F. DUNNING, President

Re Letter of May 19, 1970, concerning NDAs Nos. 8–986 and 10–144.

Dr. CHARLES C. EDWARDS,
Commissioner of Food and Drugs,
Food and Drug Administration,
200 C Street SW.,
Washington, D.C. 20204.

DEAR DOCTOR EDWARDS: On March 22, 1969, Dr. Herbert L. Ley, them Commissioner of Food and Drugs caused to be published in the Federal Register (34 F.R. 5556), a notice of Opportunity for Hearing on the proposal of the former Commissioner, Dr. Goddard, (33 F.R. 7701), to withdraw the new drug applications for Lutrexin and Trexinest, products marketed by Hynson, Westcott and Dunning, Incorporated (HW&D). By letter

dated April 18, 1969, HW&D filed a written appearance electing to avail itself of the offered opportunity for a hearing, reserving its right to contest the jurisidction of the FDA over the drugs under the provisions of Section 505 of the Federal Food, Drug and Cosmetic Act, as amended.

In your letter of May 19, 1970, to HW&D, you stated that HW&D should within thirty days after receipt of the letter, file with the hearing clerk an "amendment" of its "request" for a hearing on the proposal to withdraw the new drug applications for Lutrexin and Trexinest, and that the "request" as amended should comply with the newly issued substantial evidence regulations of May 8, 1970, which set forth new conditions for obtaining a hearing and new provisions purporting to define the term "adequate and well-controlled investigations", as used in the definition of "substantial evidence" in Section 505(d) of the Act. Thus, you stated that the "amended request" should set forth "specific facts showing that there is a genuine and substantial issue of fact that requires a hearing".

HW&D respectfully declines to submit any further appearances or a "request" for a hearing, on the grounds that the company is entitled to a hearing under the Act and has complied with the regulations of the FDA concerning the right to a hearing which were in effect when it accepted the offer of a hearing made by Commissioner Ley. Moreover, in your letter to me (undated) received on May 14, 1970, it was stated that the data submitted by HW&D "do not provide substantial evidence of effectiveness" of Lutrexin and Trexinest. Since the matter has already been judged, we can see no value in following the course which you suggest in your letter of May 19, entirely aside from the question of the validity of the regulations as applied to Lutrexin and Trexinest.

As you are aware, HW&D has filed an action against the Secretary of HEW and the Commissioner of Food and Drugs for a declaratory judgment and injunctive relief (Civil Action No. 21112, United States District Court for the District of Maryland). If HW&D should prevail in that proceeding the question of whether a hearing should be held by FDA would be moot.

On May 26, 1970, counsel for HW&D and the Government met informally with Judge Northrop of the United States Dis-

trict Court in Baltimore. Judge Northrop set the hearing on the Government's motions to dismiss and for summary judgment in the action brought by HW&D, for September 4, 1970. Mr. Goodrich, representing the Food and Drug Administration, stated that while FDA would not agree to an injunction prohibiting government action against plaintiff or its products pending disposition of the motions in the Baltimore action, the agency would not, pending such disposition, undertake proceedings looking to withdrawal of the NDAs for Lutrexin and Trexinest under Section 505(e)(3) of the Act.

Very truly yours,

Hynson, Westcott & Dunning, Inc.
(S) By: J. H. Fitzgerald Dunning,
J. H. FITZGERALD DUNNING.

Order of Dismissal

This case came on for argument on September 4, 1970, on the defendants' motion to dismiss and in the alternative for summary judgment, and counsel for the parties having been heard, first on the plaintiff's motion for continuance and then on defendants' motion for dismissal and the court being fully advised, it is this 16th day of September, 1970.

Ordered, that the motion for continuance is denied on the ground that the case was set for argument several weeks ago and contrary to the plaintiff's representations there is no cause for delay based upon new arguments advanced by the defendants, and it is further

Ordered, that the defendants' alternative motion for summary judgment is denied, and that the defendants' motion for dismissal is granted, for the reasons that the issues presented to the court are within the primary jurisdiction of the Secretary of Health, Education, and Welfare, the plaintiff has failed to exhaust its administrative remedies through which the plaintiff will be enabled to obtain an Agency determination on the record made before the Agency on the medical issues involved, on its claim that the drugs involved are generally recognized among qualified experts as safe and effective for their intended uses, its claim that they are protected from the drug efficacy review by the Grandfather Clause of the 1962 Amendments, and the claim that there is substantial evidence available to

support the therapeutic effectiveness for which the drugs are promoted. Review of the final Agency action will be available in the Courts of Appeals.

The Clerk is directed to withdraw the Order of Sept. 11th 1970 filed herein and file this Order in lieu thereof.

Edward S. Northrop
Judge EDWARD S. NORTHROP.

Date:

(Certificate of Service Omitted in Printing)

HARTER, CALHOUN & WILLIAMS,
423 WASHINGTON BUILDING,
Washington, D.C. 20005, October 16, 1970.

DOW W. HARTER,
LEONARD J. CALHOUN (1963),
EDWARD BROWN WILLIAMS,
JAN EDWARD WILLIAMS,
(202) 628-3733.

Re Docket No. FDC-D-123; NDA No. 8-986 and 10-144.

Miss BERYL MCCULLAR,
Hearing Clerk, Food and Drug Administration,
Department of Health, Education, and Welfare,
Room 6-62, 5600 Fishers Lane, Rockville, Maryland 20852.

DEAR MISS MCCULLAR: By Notice published in the Federal Register of March 22, 1969, (34 F.R. 5556), the Commissioner of Food and Drugs offered Hynson, Westcott and Dunning, Incorporated (HW&D) an opportunity for a hearing on the proposal (33 F.R. 7701) of the Commissioner to withdraw the new drug applications for HW&D's Lutrexin tablets (NDA No. 8-986) and Trexinest tablets (NDA No. 10-144). By letter dated April 18, 1969, HW&D elected to avail itself of the opportunity for a hearing. Under the regulations of the Food and Drug Administration, HW&D had met all the requirements for an administrative hearing. Under 21 CFR 130.14(b), a hearing was to be held within 90 days after HW&D's election to accept it, unless the parties agreed otherwise.

HW&D stated in its letter, however, that "Lutrexin tablets and Trexinest tablets are not new drugs under the Federal Food, Drug, and Cosmetics Act, as amended, and without regard to

other considerations, the Drug Amendments of 1962 are not applicable to those drugs. We therefore reserve the right to contest the jurisdiction of the Commissioner and the Food and Drug Administration in the administrative proceedings or in judicial procedings or in both."

Thus, on August 19, 1969, HW&D filed a complaint for declaratory judgment and injunctive relief in the United States District Court for the District of Maryland (*Hynson, Westcott and Dunning, Incorporated* vs. *Finch*, C.A. No. 21112), seeking a judicial determination of the following questions: (1) whether the drug products were generally recognized as safe on or before October 9, 1962, and if so, are they for that reason exempt from the effectiveness provisions of the 1962 Amendments under the Grandfather Clause of those Amendments; and (2) whether in any event these drugs are now generally recognized as both safe and effective and for that reason are not new drugs under the definition in Section 201(p) of the Federal Food, Drug, and Cosmetic Act. No further action was taken pursuant to HW&D's April 18, 1969, election to avail itself of an opportunity for a hearing.

After a hearing in open court, Judge Northrop of the Maryland District Court on September 11, 1970, dismissed HW&D's suit on the ground that the issues presented to the court were within the primary jurisdiction of the Secretary of HEW and that HW&D had failed to exhaust its administrative remedies. The Order, a certified copy of which is attached hereto and made a part hereof, specifically provided that HW&D's administrative remedies would enable it to "obtain an agency determination on the record made before the Agency on the medical issues involved, on its claim that the drugs involved are generally recognized among qualified experts as safe and effective for their intended uses, its claim that they are protected from the drug efficacy review by the Grandfather Clause of the 1962 Amendments, and the claim that there is substantial evidence available to support the therapeutic effectiveness for which the drugs are promoted. Review of the final Agency action will be available in the Court of Appeals."

Pursuant to the Order of the court in *Hynson, Westcott and Dunning, Incorporated* vs. *Finch*, HW&D hereby requests that the Commissioner of Food and Drugs initiate the procedures

for an administrative hearing pursuant to Part 130.14 et seq. as constituted at the time of acceptance by HW&D of an opportunity for a hearing (April 18, 1969), whereby a hearing will be held on the question of the proposal of the FDA to withdraw the new drug applications for Lutrexin and Trexinest on the ground that new information before the Commissioner with respect to such drugs, evaluated together with the evidence available to him when the applications were approved, shows there is a lack of substantial evidence of effectiveness of the drugs.

Further, pursuant to the Order of the court in *Hynson, Westcott and Dunning, Incorporated* vs. *Finch*, a hearing is requested on the following questions which the court held were within the primary jurisdiction of the FDA and must be determined on the record by the agency:

(1) Whether after the new drug applications (NDAs) for Lutrexin and Trexinest became effective in 1953 and 1956 respectively, those drugs became, prior to October 10, 1962, generally recognized by qualified experts as safe for use under the conditions stated in their labeling and have been used to a material extent and for a material time under such conditions (other than in investigations to determine their safety and effectiveness), within the meaning of Section 201(p) of the Federal Food, Drug, and Cosmetic Act, and are for that reason exempt from the Drug Amendments of 1962, by the Grandfather Clause contained in Section 107(c) of the Amendments.

(2) Whether Lutrexin and Trexinest are now generally recognized by qualified experts as safe and effective for use under the conditions stated in their labeling and have been used to a material extent and for a material time under such conditions (other than in investigations to determine their safety and effectiveness), within the meaning of the definition of new drugs contained in Section 201(p) of the Federal Food, Drug, and Cosmetic Act as amended.

I. Substantial Evidence—Supporting Data

The data listed below have heretofore been submitted to FDA pursuant to the Drug Efficacy Study Implementation Announcement (33 F.R. 7701), in support of HW&D's position that there is substantial evidence of effectiveness of Lutrexin for its indicated uses, and such data is incorporated herein by reference:

1. Data submitted in connection with New Drug Application for Lutrexin tablets which became effective in 1953.

2. August 20, 1965—Dr. J. H. F. Dunning's letter to Mr. G. P. Larrick., Commissioner, re Lutrexin literature being submitted to Drug Efficacy Study Group of NAS-NRC.

Enclosures:

(a) Lutrexin labelling.

(b) Lutrexin package insert.

(c) Lutrexin bibliography.

(d) Lutrexin published reprints and abstracts.

(e) Lutrexin New and Non-Official Remedies Publications, 1955 to 1962.

3. August 20, 1965—Dr. J. H. F. Dunning's letter to Mr. G. P. Larrick, Commissioner, re Trexinest literature being submitted to Drug Efficacy Study Group of NAS-NRC.

Enclosures:

(a) Trexinest labelling.

(b) Trexinest package insert.

(c) Trexinest published reprints and abstracts.

4. August 30, 1966—Dr. C. A. Dunning's letter, with NAS Drug Efficacy Study Form on Trexinest Tablets.

5. September 6, 1966—NAS Submission.

Enclosures:

(a) Rizzolo reprint, "A Uterine Relaxant for Premature Uterine Contractions".

(b) Lutrexin bibliography.

(c) Supporting letter on Lutrexin from Dr. Braun. Sheboygan Clinic, Sheboygan, Wisconsin.

6. July 12, 1968—Messrs. John K. Worley/Bruce J. Brennan's letter to Dr. Paul A. Bryan, responding to Drug efficacy Study Implementation Announcement published in the Federal Register, May 24, 1968.

7. July 18, 1968—Messrs. Bruce J. Brennan/John K. Worley's letter to Dr. H. L. Ley, re submitting data within time period set forth in May 24, 1968, Announcement.

Enclosure:

Messrs. Worley/Brennan's letter of July 12.

8. July 22, 1968—Mr. G. F. Whattam's letter to Dr. Paul A. Bryan re consideration of extension until September 15, 1968.

Enclosures:

(a) Dr. Grattons' paper.

(b) Jeremias & Trythall paper, April 1962 Meet. of Inter. Fertility Assoc.

(c) Curriculum vitae on Drs. Gratton, Majewski, Rezek, and Trythall.

9. July 26, 1968—Messrs. Bruce J. Brennan/John K. Worley's letter to Dr. H. L. Ley, Jr., re FDA's refusal to grant HW&D request for extension. Request for reconsideration.

10. November 22, 1968—Lutrexin Submission to FDA.

Enclosures:

(a) Dr. J. H. F. Dunning's letter to Commissioner G. P. Larrick of August 20, 1965, re Lutrexin.

(b) Dr. J. H. F. Dunning's letter to Commissioner G. P. Larrick of August 20, 1965, re Trexinest.

(c) Curriculum vitae on Dr. R. L. DiBenedetto, Baton Rouge, Louisiana.

(d) Paper by Dr. DiBenedetto, "Treatment of Premature Labor in Clinic Patients".

(e) Curriculum vitae on Dr. F. B. Gray, Grand Rapids, Michigan.

(f) Paper by Dr. Gray, "Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases".

(g) Curriculum vitae on Dr. J. T. Majewski, Milwauke, Wisconsin.

(h) Paper by Dr. Majewski, "Statistical Evaluation in the Reduction of the Incidence of Prematurity".

(i) Curriculum vitae on Dr. G. H. Rezek, Cicero, Illinois.

(j) Paper by Dr. Rezek, "A Summary of Case Findings Over a 10 Year Period".

(k) Curriculum vitae on Dr. R. W. Vera, Southfield, Michigan.

(l) Lutrexin Case Records by Dr. Vera, "The Use of Lutrexin in Reducing Uterine Irritability and Neonatal Deaths Caused by Premature Labor. A Description of 22 Cases".

(m) Paper by Dr. John W. Huffman, Chicago, "From Menarche to Maturity. A Gynecologist's Approach", Postgraduate Medicine, June 1968.

(n) Paper by Dr. G. H. Rezek, "Uterine Motility and the Survival of the Fetus", Medical Digest Bombay 4, July 1963.

(o) Supporting letters from: Dr. J. R. Allan, Excelsior Springs, Missouri; Dr. R. G. Barrick, Chicago, Illinois; Dr. W. M. Bickers, Beirut, Lebanon; Dr. B. D. Coleman, Augusta, Georgia; Dr. E. A. Chandler, Houston, Texas; Dr. I. Goldberg, Augusta, Georgia; Dr. H. A. Bollin, Chicago, Illinois; Dr. Bernard Gomberg, Bellevue, Washington; Dr. H. Hoffman Groskloss, Miami, Florida; Dr. J. M. Haws, Baltimore, Maryland; Dr. Grey Jones, St. Louis, Missouri; Dr. R. A. McDermott, Jr., Chicago, Illinois; Dr. P. H. Muskie, Dearborn, Michigan; Dr. G. P. Nolan, Westminster, California; Dr. W. F. Peterson, USAF, Andrews AFB, Washington, DC; Dr. C. L. Randall, Buffalo, New York; Dr. H. A. Ritter, St. Louis, Missouri; Dr. R. T. F. Schmidt, Cincinnati, Ohio; Dr. M. D. Sims, South Miami, Florida.

11. April 18, 1969—Dr. J. H. F. Dunning's letter to Miss B. S. McCullar, Hearing Clerk, Office of General Counsel, electing opportunity for a hearing.

It is submitted that these data constitute substantial evidence of the effectiveness of Lutrexin for its indicated uses. HW&D is entitled to a hearing under the regulations as framed on April 18, 1969, and has fully complied with the requirements of those regulations. It is our position that the May 8, 1970, substantial evidence regulations cannot legally be

applied to this proceeding, and that the regulations are legally invalid in many crucial respects. Assuming, arguendo, their applicability, however, the data listed above constitute "substantial evidence" as defined in the May 8, 1970 regulations and are legally sufficient to warrant the holding of an administrative hearing on the question of the substantial evidence of Lutrexin.

In any event, the new evidence in the form of affidavits and other data, attached hereto and listed under Part 2 herein, clearly demonstrate that there is substantial evidence of effectiveness of Lutrexin under the May 8, 1970 regulations. This evidence at the least requires that the FDA hold a hearing on its proposal to withdraw the new drug application for Lutrexin.

II. Jurisdictional Questions—Supporting Data

The following data are submitted in support of HW&D's request for a hearing on the jurisdictional questions posed above. With the exception of the affidavit of Dr. Sylvester W. Trythall, the data were before the court in *Hynson, Westcott and Dunning, Inc.* vs. *Finch.*

This request for a hearing on the jurisdictional issues is made pursuant to the Court's Order in the *Finch case.* The hearing would involve substantive questions of fact concerning general recognition of safety and effectiveness. These factual questions can only be decided on the record after an adjudicatory hearing before the Food and Drug Administration. The matters of substantial evidence and the applicability of the May 8, 1970 regulations are relevant only to the hearing requested under Part I of this letter and not to this request for a hearing on the jurisdictional questions. We can therefore see no basis for denial of this request. If Luxtrexin were, after a hearing, found not to be a "new drug", or not to be subject to the Drug Amendments of 1962, the questions of substantial evidence and the applicability of the May 8, 1970 regulations would be moot.

A listing of the data submitted herewith follows:

1. HW&D's Complaint for Declaratory Judgment and Injunctive Relief in *Hynson, Westcott and Dunning, Incorporated* vs. *Finch,* CA No. 21112, including three exhibits: Drug Efficacy Study Implementation (33 F.R.

7701), Notice of Opportunity for Hearing (34 F.R. 5556), and letter of HW&D electing to avail itself of opportunity for a hearing, dated April 18, 1969.

2. HW&D's Memorandum in Opposition to Defendants' Motions to Dismiss and in the Alternative for Summary Judgment (CA No. 21112), with the following exhibits:

(a) Exhibit I. Affidavit of William M. Bickers, M.D., with curriculum vitae (Exhibit A) and list of publications.

(b) Exhibit II. Affidavit of Richard R. Gratton, M.D., with curriculum vitae (Exhibit A) and a true copy of paper by Dr. Gratton entitled "Treatment of Infertility and Prematurity Pregnancy Problems".

(c) Exhibit III. Affidavit of Fred B. Gray, M.D., with clinical report entitled: "Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases".

(d) Exhibit IV. Affidavit of Joseph T. Majewski, M.D., with curriculum vitae and list of publications (Exhibit A), and true copies (Exhibits B, C, and D) of papers by Dr. Majewski, entitled: "A Uterine Relaxing Factor for Premature Labor", "Further Experiences with a Uterine-Relaxing Hormone in Premature Labor", and "Statistical Evaluation in the Reduction of the Incidence of Prematurity".

(e) Exhibit V. Affidavit of George H. Rezek, M.D., with curriculum vitae and list of publications (Exhibit A), and true copies of two pages (Exhibits B and C) by Dr. Rezek entitled: "The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea" and "Lutrexin in the Treatment of Premature Labor".

(f) Exhibit VI. Affidavit of Joseph F. Sadusk, M.D., with curriculum vitae (Exhibit A), list of publications (Exhibit B), and true copy of paper Exhibit C) by Dr. Sadusk entitled: "The Definition of the Efficacy of a Drug Under the Law".

(g) Exhibit VII. Copy of letter dated January 22, 1970, from HW&D to Commissioner Edwards, with copy of letter dated December 10, 1969, from Willard

M. Allen, M.D., to J. H. F. Dunning, President of HW&D (Exhibit A).

(h) Exhibit VIII. Commissioner Edwards' reply, undated, to Dr. Dunning's letter of January 22, 1970.

3. Copy of Motion of Plaintiff for Continuance.

4. Affidavit of Sylvester W. Trythall, M.D., dated September 14, 1970, with curriculum vitae and list of publications.

5. Letter dated May 19, 1970, from Commissioner Edwards to HW&D.

6. Letter dated June 10, 1970, from J. H. F. Dunning to Commissioner Edwards.

7. True copy of Transcript of Hearing on Defendants' Motions to Dismiss and in the Alternative for Summary Judgment in CA No. 21112 (D. Md.), on September 4, 1970.

8. Certified copy of Order of Dismissal in CA No. 21112 (D. Md.), September 11, 1970.

Respectfully submitted,

(s) Edward Brown Williams
EDWARD BROWN WILLIAMS,
Counsel for Hynson, Westcott and Dunning, Incorporated.

EBW: fh.
Enclosures.

Affidavit of William M. Bickers, M.D. in Support of Plaintiff's Memorandum in Opposition to Defendants' Motion To Dismiss and in the Alternative for Summary Judgment

William M. Bickers, being duly sworn, deposes and says:

1. I make this affidavit in support of plaintiff's memorandum in opposition to defendants' motion to dismiss and in the alternative for summary judgment, filed herewith in the above-captioned cause.

2. I am a physician engaged in the practice of obstetrics and gynecology in Richmond, Virginia, and Beirut, Lebanon. I received an M.D. degree from The Medical College of Virginia

in 1933, and was licensed to practice medicine in Virginia in 1933. I am a Diplomate of the American Board of Obstetrics and Gynecology, the American Fertility Society, and the Society for the Study of Sterility.

3. I am presently, and have been since 1960, professor and chairman of the Department of Obstetrics and Gynecology, The American University Hospital, Beirut, Lebanon. I spend nine months of the year in Beirut and two to three months in Richmond, Virginia, where I, with my associate, maintain an active OB/GYN practice. I have authored approximately fifty-eight papers dealing with obstetrics and gynecology as well as two textbooks on the subject. A copy of my curriculum vitae is attached hereto as Exhibit A. I am familiar with the scientific literature in the OB/GYN field including that concerning Lutrexin, and keep myself currently informed by the study of such literature, attendance at meetings of professional societies, and consultation with OB/GYN specialists.

4. I commenced using Lutrexin Tablets for dysmenorrhea, and second and third trimester threatened abortion in 1953, and have used the drug for these indications in my practice in Richmond up to the present time. Hynson, Westcott & Dunning, Incorporated does not have a representative in Beirut, and consequently, Lutrexin is not available there. I have in my practice prescribed Lutrexin for over three hundred patients with pregnancy problems, and over one thousand patients with dysmenorrhea.

5. Clinical experience such as my own in the use of Lutrexin in treatment of dysmenorrhea and premature labor, as well as studies such as those preformed by Drs. J. T. Majewski and G. H. Rezek (Majewski and Jennings: *Uterine Relaxing Factor for Premature Labor,* OB & GYN., 5:649–652, May 1955, and *Further Experiences with a Uterine Relaxing Hormone in Premature Labor,* OB & GYN., 9:322–325, March, 1957; Rezek, *The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea,* AM. J. OB & GYN., 66:396–402, August, 1953, and *Lutrexin in the Treatment of Premature Labor,* Annals of New York Academy of Sciences, 75:995–997, January, 1959) show the effectiveness and safety of Lutrexin and cannot be ignored on the ground they are not double-blind placebo type investigations. The

difficulties concomitant with the performance of this type of study of a drug for use in conditions with a high risk of fatality are well known. Accordingly, clinical studies of the type cited, together with clinical experience must, of necessity, be considered.

6. I have studied the report of the panel of the National Academy of Sciences-National Research Council which evaluated Lutrexin as "possibly effective" in the treatment of dysmenorrhea and threatened abortion, and understand that the Food and Drug Administration, subsequent to the report, has proposed to remove Lutrexin from the physician's armamentarium. I have also reviewed the data of Hynson, Westcott and Dunning, Incorporated submitted to the Food and Drug Administration in response to the proposed removal of the drug from the market.

7. Based upon my experience in obstetrics and gynecology and with the use of Lutrexin in that practice, set forth above, it is my opinion that the drug is therapeutically effective in the treatment of dysmenorrhea and second and third trimester threatened abortion. Further, the safety of Lutrexin is subject to no question; I have prescribed up to four tablets per day (12,000 units) for dysmenorrhea and labor difficulties, and have found no side effects of any significance whatever. Lutrexin is a valuable drug in these cases and is the only effective agent available to the OB/GYN practitioner faced with the problem of an excessively irritable uterus.

8. Based upon my experience, summarized above, discussions with OB/GYN colleagues, and upon my knowledge of the literature, it is my opinion that Lutrexin is generally recognized by OB/GYN physicians as safe and effective for use in the treatment of cases of dysmenorrhea and second and third trimester threatened abortion under the conditions recommended in its labeling. Upon the same basis it is my opinion that the safety of Lutrexin has been generally recognized by such physicians for such uses for at least ten years.

I am prepared to testify as to these matters in court.

(S) William M. Bickers

WILLIAM M. BICKERS, M. D.

REPUBLIC OF LEBANON, CITY OF BEIRUT,
EMBASSY OF THE UNITED STATES OF AMERICA, *ss:*

Subscribed and sworn to before me Thomas B. Killeen, Vice Consul of the United States of America, at Beirut, Lebanon, duly commissioned and qualified on 12th day of March, 1970.

(S) Thomas B. Killeen,
THOMAS B. KILLEEN,
American Vice Consul.

Date: March 12, 1970.

[Exhibit A]

PROFESSIONAL STATISTICS

DR. WILLIAM M. BICKERS, *412 Medical Arts Building, Richmond, Virginia 23217.*
Year of Birth: 1908.
Medical Education: Medical College of Virginia, Richmond, M.D. Degree, 1933.
Year of License: 1933, State of Virginia.
American Specialty Board: American Board of Obstetrics and Gynecology.
Primary Specialty: Obstetrics and Gynecology.
Type of Practice: Full time specialty practice.
Internship: 1933–34, Medical College of Virginia.
Residency: Obstetrics & Gynecology, Boston City Hospital, 1934–35.
Professorial Appointment: Instructor, Gynecology, Medical College of Virginia, 1936–49.
Professor and Chairman of the Department of Obstetrics & Gynecology, American University, Beirut, 1945–46, 1960—
Professional Societies:
American Medical Association.
American Association of Obstetrics & Gynecology.
American Fertility Society.
American Association for the Advancement of Sciences.
Endocrinology Society.
Society for the Study of Sterility.
Pan-am. Cancer Cytol. Soc. Endocrinology.
Society for the Study of Uterine Muscle Physiology.

Affidavit of Richard R. Gratton, M.D. in Support of Plaintiff's Memorandum in Opposition to Defendants' Motion To Dismiss and in the Alternative for Summary Judgment

Richard R. Gratton, M.D., being first duly sworn, deposes and says:

1. I received an M.D. degree from the Stanford University School of Medicine, Palo Alto, California in 1944, and was licensed to practice medicine in California in 1947. My primary specialty is obstetrics and gynecology. I am a fellow of the American College of Obstetricians and Gynecologists, a member of the American Society of Abdominal Surgeons, and a past member of the International Fertility Association. A copy of my curriculum vitae is attached hereto as Exhibit A.

2. My practice deals primarily with what may be termed a subspecialty of OB/GYN practice, i.e., the treatment of infertility or habitual abortion. The majority of the patients I treat are pregnant women (or those who contemplate pregnancy), who have been referred to me by other physicians and who have a history of from one to ten previous miscarriages, spontaneous abortions, or premature deliveries. I have been engaged in this specialty for nineteen years, and have treated one thousand and thirty-six patients for this affliction. I am familiar with the scientific literature in OB/GYN, including that concerning Lutrexin, and keep myself currently informed by the study of such literature, attendance at meetings of professional societies, and consultation with OB/GYN specialists.

3. I have had extensive experience in the use of Lutrexin tablets manufactured by Hynson, Westcott and Dunning, Inc., having administered the drug to more than one thousand women with a history of pregnancy complications, over a period of fourteen years. I have attached hereto as Exhibit B a copy of my paper entitled *The Treatment of Infertility and Prematurity Pregnancy Problems* (1968, unpublished). In this study are reported the results of Lutrexin therapy in 219 habitual aborters.

4. I have reviewed the report of the panel of the National Academy of Sciences-National Research Council which evalu-

ated Lutrexin as "possibly effective" in treatment of premature labor and habitual abortion, and I have been informed that the Food and Drug Administration has, because of the report, proposed to remove Lutrexin from the market. I have also reviewed the data of Hynson, Westcott and Dunning, Inc. submitted to FDA in response to the proposed removal of the drug from the market.

5. Based on my experience with Lutrexin, above-outlined, it is my opinion that Lutrexin is an effective agent in the treatment of habitual abortion and premature labor. Moreover, there is no question that Lutrexin is safe, for I have administered up to 36,000 units of the drug to many patients in an eight to twenty-four-hour period with no side effects to mother or child. It is my firm belief that removal of Lutrexin from the physician's armamentarium would be a grievous error. Lutrexin has proved invaluable to me in my practice which involves patients who have repeatedly faced the tragedy of premature expulsion of a non-viable fetus. Although progestational agents are useful in the first trimester of pregnancy, there is no product other than Lutrexin which is effective in producing quiescence of the uterus in the second and third trimester of pregnancy as well as in the first trimester. As stated in the attached study, prior to institution of the use of Lutrexin as the major drug in treating infertility cases, less than 50 per cent viable babies resulted. With the use of Lutrexin 80 per cent viable babies were obtained.

6. Studies such as the one reported in Exhibit B, utilizing the past histories of the patients as controls, together with the clinical experience of the physician, are proof of the effectiveness of Lutrexin. Such studies of and experience with a drug cannot be dismissed on the ground that they are valueless because they do not use a double-blind placebo type of investigation. The latter type of investigation is inconceivable from the standpoint of ethics and morality where, as here, there exists a high risk of mortality and the physician is testing a drug (Lutrexin) which is clinically-proven to be effective.

7. Based upon my experience, summarized above, discussions with OB/GYN colleagues and my knowledge of the literature, it is my opinion that Lutrexin is generally recognized by OB/GYN physicians as safe and effective for use in the treatment of cases of habitual abortion and premature labor under

the conditions recommended in its labeling. Upon the same basis, it is my opinion that the safety of Lutrexin has been generally recognized by such physicians for such uses for at least ten years.

8. I am prepared to testify as to these matters and give supporting data to my opinions expressed above in a proceeding in court or at a hearing before the Food and Drug Administration.

(S) Richard R. Gratton, M.D.
RICHARD R. GRATTON, M.D.

Subscribed and sworn to before me this 12th day of March, 1970.

(S) MARJORIE S. HAMBURGER,
Notary Public.

[Exhibit A]

PROFESSIONAL STATISTICS

DR. RICHARD R. GRATTON,
490 Post Street,
San Francisco, California 94102
Year of Birth: 1915.
Medical Education: Stanford University School of Medicine, Palo Alto, California, M.D. Degree in 1944.
Year of License: 1947.
Primary Specialty: Obstretics and Gynecology.
Type of Practice: Full time specialty practice.
Internship and Residence:
U.S. Naval Hospital, Mare Island, California 1943–44.
All Ob-Gyn Interne 1947–48.
Assistant Resident 1948–49.
Senior Assistant Resident 1949–50.
Resident 1950–51, Stanford University Hospital.
Teaching Affiliation:
Teaching Assistant Ob/Gyn, Sanford Medical School.
Lecturer in Ob, Stanford School of Nursing.
Hospital Affiliation:
Stanford University Hospital.
St. Francis Memorial Hospital.
Childrens Hospital.

St. Joseph Hospital.
St. Marys Hospital.
Franklin Hospital.

Membership:

American College of Obstreticians and Gynecologists.
American Society of Abdominal Surgeons.

Papers:

Haman, J. O. and Gratton, R. R.; The Obstreticians Responsibility to the Previously Infertile Patient, Proceedings of the Second World Congress on Fertility & Sterility, 1956.

Gratton, R. R., and Thelander, H. E.: A Developmental Study of Triplets, Journal Amer. Med. Wom. Assoc. *16*: 445–9, June 1961.

Gratton, R. R.: The Treatment of Infertility and Prematurity Pregnancy Problems, (1968 Unpublished).

The undersigned hereby certifies that the foregoing is a true and correct statement of his professional qualifications.

(S) Richard R. Gratton, M.D.
RICHARD R. GRATTON, M.D.

Date 6 March 1970.

Affidavit of Joseph T. Majewski, M.D., in Support of Plaintiff's Memorandum in Opposition to Defendants' Motion To Dismiss and in the Alternative for Summary Judgment

Joseph T. Majewski, being first duly sworn, deposes and says:

1. I make this affidavit in support of plaintiff's memorandum in opposition to defendants' motion to dismiss and in the alternative for summary judgment, filed herewith in the above-entitled cause.

2. I received an M.D. degree from Marquette University School of Medicine in 1945, and was licensed to practice medicine in Wisconsin in 1948. My specialty is obstetrics and gynecology and I am certified by the American Board of Obstetrics and Gynecology. I am also a fellow of the American College

of Obstetricians and Gynecologists. A copy of my curriculum vitae is attached hereto as Exhibit A.

3. I have engaged in the active practice of obstetrics and gynecology for eighteen years, and have used Lutrexin in the treatment of cases of threatened abortion and premature labor for more than fourteen years. I have administered Lutrexin to more than three hundred women to prevent premature delivery of the infant. I am familiar with the scientific literature dealing with threatened abortion and premature labor, including that concerning Lutrexin. I keep myself currently informed by the study of such literature, attendance at meeting of professional societies, and consultation with colleagues.

4. I have written three papers (copies of which are attached hereto as exhibits) reported the results of administration of Lutrexin in cases of premature labor, *viz.*, (Exhibit B) Majewski and Jennings, *A Uterine Relaxing Factor for Premature Labor,* Obstetrics and Gynecology, Vol. 5, No. 5, 649 (May, 1955); (Exhibit C) Majewski and Jennings, *Further Experiences With A Uterine Relaxing Hormone in Premature Labor,* Obstetrics and Gynecology, Vol. 9, No. 3, 322 (March, 1957); and (Exhibit D) Majewski, *Statistical Evaluation in the Reduction of the Incidence of Prematurity* (1968, unpublished).

5. I have reviewed the report of the panel of the National Academy of Sciences-National Research Council which found Lutrexin to be "possibly effective" in the treatment of threatened abortion and premature labor, and understand that the Food and Drug Administration has moved to take Lutrexin off the market, subsequent to this "possibly effective" evaluation. In addition, I have reviewed the data of Hynson, Westcott and Dunning submitted to FDA in response to the proposed removal of Lutrexin from the market.

6. It is my opinion, based upon my experience with Lutrexin, the pertinent scientific literature, and the contacts mentioned in paragraph 3 above, that Lutrexin is effective in the treatment of cases of threatened abortion and premature labor. I have found, in my practice, no other effective therapeutic agent for these indications. The safety of Lutrexin, not only in the dosage suggested in the drug's labeling but in amounts substantially in excess thereof, is beyond dispute. I have frequently administered 4000 units of the drug stat., and 1000 units hourly thereafter

until Uterine contractions cease, and have never encountered any adverse effects in either mother or infant. Removal of Lutrexin from the OB/GYN's armamentarium would in my opinion border on the criminal, for, as shown in my 1968 study (Exhibit D), before treatment with Lutrexin, 75 patients, with 210 pregnancies, delivered only 109 live infants (52 per cent). The same 75 women on Lutrexin therapy produced 65 live children out of a total of 75 pregnancies (86 per cent).

7. The method of investigation utilized in my studies (Exhibit B, C, and D) *viz.*, use of the patients as their own controls, or use as a control of statistics reflecting the experience with other patients with no treatment, together with the general clinical experience of the physician, constitute the only humane approach to the study of the effectiveness of a drug for use in threatened abortion and premature labor. These complications of pregnancy carry a high risk to the life of the fetus and perhaps the mother. Use under such conditions of a double-blind, placebo type of investigation would be unethical and immoral, where, as here, there exists a drug (Lutrexin) clinically-proven to be of value in the treatment of the affliction involved.

8. Based upon my experience, communications with OB/GYN practitioners in Wisconsin and elsewhere concerning Lutrexin and upon my knowledge of the literature relating to the drug and the conditions of its use, it is my opinion that Lutrexin is generally recognized by OB/GYN physicians as both safe and effective in treatment of threatened abortion and premature labor under the conditions of use recommended in its labeling. Upon the same basis it is my opinion that the safety of Lutrexin has been generally recognized for such use under such conditions by OB/GYN physicians for at least ten years.

9. I am prepared to testify as to these matters, and to present data to support the opinions expressed above, in a proceeding in court or before the Food and Drug Administration.

/s/ Joseph T. Majewski, M.D.
JOSEPH T. MAJEWSKI, M.D.

Subscribed and sworn to before me this 5th day of March, 1970.

(S) JOHN G. MALONEY,
Notary Public,
Comm. Exp. 10–4–70.

495-151—73 ——1

[Exhibit A]

Professional Statistics

Name: Joseph T. Majewski.

Office Address: 10425 West North Avenue, Milwaukee, Wisconsin.

Date of Birth: 1922, Milwaukee, Wisconsin.

Curriculum Vitae:

1945, M.D. degree, Marquette University School of Medicine, Milwaukee, Wisconsin.

1945–46, Intern, U.S. Navy Hospital, Farragut, Idaho.

1946–48, Lt. (jg) USNR.

1948–51, Resident, Lewis Memorial Maternity Hospital.

19—, Clinical Instructor, Department of Obstetrics and Gynecology, Marquette, University School of Medicine.

19—, Att. Staff, St. Joseph Hospital and Evangelical Deaconess Hospital, Milwaukee, Wisconsin; Courtesy Staff, Milwaukee Hospital; Att. Staff, Milwaukee County General Hospital.

Certification: 1948, License to practice medicine 1955, American Board of Obstetrics and Gynecology.

Private Specialty: Obstetrics and Gynecology.

Type of Practice: Full-time specialty practice.

Membership in Professional Societies:

American Medical Association.

American Association of Obstetrics and Gynecology.

Central Association of Obstetrics and Gynecology.

American College of Obstetricians and Gynecologists.

Papers:

Majewski, J.: Stab Wounds of Heart; 2 cases, Polski Tygodnik Lik, *2*:390–393, 1947.

Schmitz, H. E. and Majewski, J. T.: End Results in Treatment of Ovarian Carcinoma With Surgery and Deep X-Ray Irradiation, Radiology, *57*:820–825, December 1951.

Majewski, J. T. and Jennings, T.: Uterine Relaxing Facts for Premature Labor, Obst. & Gynec., *5*:659–652, May 1955.

Majewski, J. T. and Jennings, T.: Further Experience with a Uterine-Relaxing Hormone in Premature Labor, Obst. & Gynec., *9*:322–325, March 1957.

Majewski, J. T.: Statistical Evaluation in the Reduction of the Incidence of Prematurity, 1968, unpublished.

CERTIFICATE

The undersigned hereby certifies that the foregoing is a true and correct statement of his professional qualifications.

(S) J. T. Majewski, M.D.
J. T. MAJEWSKI, M.D.

Date: March 5, 1970.

Affidavit of George H. Rezek, M.D. in Support of Plaintiff's Memorandum in Opposition to Defendants' Motion To Dismiss and in the Alternative for Summary Judgment

George H. Rezek, being first duly sworn, deposes and says:

1. I make this affidavit in support of plaintiff's memorandum in opposition to defendants' motion to dismiss and in the alternative for summary judgment, filed herewith in the above-entitled cause.

2. I am a physician engaged in the practice of obstetrics and gynecology in the State of Illinois. I received an M.D. degree from the University of Illinois in 1932, and am licensed to practice medicine in that State. I am a Diplomate of the American Board of Obstetrics and Gynecology and a Fellow of the American College of Obstetricians and Gynecologists, the American College of Surgeons and The International College of Surgeons. I am also a member of the Chicago Gynecological Society. A copy of my curriculum vitae is attached hereto (Exhibit A).

3. I have been practicing OB/GYN for thirty-six years, with particular emphasis upon medical problems involved with premature labor and menstrual disorders. I have done extensive research in these areas, having for thirty-five years studied uterine motility as applied to premature labor and prevention of menstrual disorders.

I am familiar with the extensive scientific literature in those areas, including that concerning Lutrexin, and keep myself currently informed by the study of such literature, attendance at meetings of professional societies, and consultation with OB/GYN specialists.

I have published and collaborated in the publication of five papers on these subjects (listed in Exhibit A).

4. I have used Lutrexin in the treatment of dysmenorrhea and premature labor for approximately twenty years and have administered the drug to approximately five hundred women afflicted with these disorders. Attached hereto are reprints of two published papers (Exhibits B and C, respectively) reporting the results of administration of Lutrexin in cases of dysmenorrhea and premature labor, *viz.*, Rezek, *The Effect of A New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea*, American Journal of Obstetrics and Gynecology, Vol. 66, No. 2, p. 396, August, 1953; Rezek, *Lutrexin in the Treatment of Premature Labor*, Annals of New York Academy of Sciences, Vol. 75, Art. 2, p. 995, January, 1959.

5. The method of investigation utilized in my study of the use of Lutrexin in premature labor (Exhibit C) plus my extensive clinical experience with the use of the drug in complications of pregnancy cannot be dismissed as of no value in showing the effectiveness of Lutrexin on the ground that my investigations are not well-controlled. Since the risk of death to the fetus is premature labor difficulties is high, the use of the double-blind, placebo type of study cannot be countenanced by any ethical or moral physician, where, as here, there exists a drug (Lutrexin) clinically-proven effective.

6. I have reviewed the report of the panel of the National Academy of Sciences-National Research Council which evaluated Lutrexin as "possibly effective" in the treatment of premature labor and dysmenorrhea, and understand that the Food and Drug Administration has subsequent to the report proposed to remove Lutrexin from the market. Further, I have studied the data of HW&D submitted to FDA in response to the proposed removal of Lutrexin from the market.

7. Based on my experience with Lutrexin, above outlined, it is my opinion that Lutrexin is effective in the treatment of premature labor and dysmenorrhea. It is established that Lutrexin is safe for these uses; I have prescribed up to 12,000 units hourly for seven days of the drug for patients suffering from

premature labor and dysmenorrheic difficulties, with no adverse side effects whatsoever.

8. Based upon my experience, discussions with OB/GYN colleagues concerning Lutrexin and upon my knowledge of the literature relating to the drug and the conditions of its uses, it is my opinion that Lutrexin is generally recognized by OB/GYN physicians as safe and effective for use in the treatment of cases of premature labor and dysmenorrhea under the conditions recommended in its labeling. Upon the same basis it is my opinion that Lutrexin has been generally recognized by OB/GYN physicians as safe for such use under such conditions for at least ten years.

9. I am prepared to testify in Court as to these matters and give supporting data to my opinions above-expressed.

(S) George H. Rezek, M.D.
GEORGE H. REZEK, M.D.

Subscribed and sworn to before me this 5th day of March, 1970.

(S) RUDOLPH GERMACK,
Notary Public.

EXHIBIT A

CURRICULUM VITAE

DR. GEORGE HENRY REZEK
6001 Cermak Road,
Cicero, Illinois 60650.
Year of Birth: 1905.
Medical Education: University of Illinois College of Medicine, Chicago, M.D. Degree in 1932.
Year of License: 1932, State of Illinois.
American Specialty Board: American Board of Obstetrics and Gynecology.
Primary Specialty: Obstetrics and Gynecology.
Type of Practice: Full time specialty practice.
Internship and Residence:
Research and Educational Hospital, Chicago 1932–33.

Resident in Ob/Gyn, Research and Educational Hospital 1933–36.

Teaching Affiliation: University of Illinois, Clinical Associate Professor, Ob/Gyn.

Hospital Affiliation: Chairman, Department Ob/Gyn, Garfield Park Community Hospital.

Membership:

Chicago Gynecological Society.

Fellow American College of Surgeons.

Fellow American College of Obstetricians and Gynecologists.

Fellow International College of Surgeons.

Professorial Appointment: University of Illinois College of Medicine, Chicago.

Papers Published:

Rezek, G. H.: Biologic Test for Diagnosis of Intra-uterine Fetal Death, AMER. JOUR. OBST. & GYNEC., *32*:976–981, December 1936.

Rezek, G. H. and Benesohn, S. J.: Clinical and Experimental Observations on the Use of Corpus Luteum Extracts in Obstetrics, SURG., GYNEC. & OBST., *75*:289–299, September 1942.

Rezek, G. H.: Effect of New Potent Uterine Relaxing Factor of Corpus Luteum in Treatment of Dysmenorrhea, AMER. JOUR. OBST. & GYNEC., *66*:396–402, August 1953.

Rezek, G. H.: Lutrexin in the Treatment of Premature Labor, ANN. N.Y. ACAD. SCI., *75*:995–997, January 9, 1959.

Rezek, G. H.: Uterine Motility and the Survival of the Fetus, MED. DIG., 296–297, Bombay, India, July 1963.

The undersigned hereby certifies that the above is a true and correct statement of his curriculum vitae

(S) George H. Rezek, M.D.
GEORGE HENRY REZEK, M. D.

Date: March 5, 1970.

WASHINGTON UNIVERSITY,
SCHOOL OF MEDICINE,
St. Louis, Missouri 63110, 10 December 1969.

DEPARTMENT OF
OBSTETRICS AND GYNECOLOGY,
4911 Barnes Hospital Plaza,
St. Louis, Missouri 63110.

Mr. J. H. F. DUNNING,
President, Hynson, Westcott and Dunning, Inc.,
Baltimore, Maryland.

DEAR MR. DUNNING: I certainly enjoyed seeing you again after so many years. Recalling the events of the Govt. vs. Hynson, Westcott and Dunning (?1940) took us back to our more youthful days. The issues then were much the same as the issues today: how far should the FDA go in controlling the medications available to physicians for the treatment of patients? The Judge, if you recall, said at the opening of the trial that he was sure that the Government would present evidence that the Lutein Tablets were ineffectual and that Hynson, Westcott and Dunning would present evidence that the medication was efficacious.

The situation regarding Lutrexin today is not quite the same. Lutrexin contains a biologically active component (as yet unidentified structurally) which has a relaxing effect on the uterus of the laboratory animals and women.

The NRC panel considered Lutrexin as possibly effective. This opinion of the panel does not mean that Lutrexin may possibly contain an active component. It means, on the contrary, that Lutrexin may be possibly effective in the conditions for which it is recommended, i.e., dysmenorrhea, threatened abortion or premature labor. The situation today is much the same, however, as 30 years ago in that the FDA seems to be interpreting 'possibly effective' as ineffective and, once more, the clinical evidence becomes of paramount importance.

The clinical evidence which you have submitted, and which I have read carefully, does indicate that Lutrexin is beneficial in the three conditions for which it is recommended. The evidence also indicates that Lutrexin is not harmful or dangerous either to the patient or to the fetus. You have submitted no evidence that Lutrexin is ineffective, nor do I know of any evidence in the medical literature indicating that it is ineffective. Lutrexin is recommended, for example, in premature labor. Uterine contractility is essential for delivery of the child but when uterine contractility comes prematurely the child may be lost from prematurity. Women have been forced to face the tragedy of premature labor for centuries because medical science has not provided as yet a complete explanation for premature labor, nor has medical science provided a scientifically rational method for preventing premature labor, or for stopping premature labor once it has started. A great deal is known, of course, concerning the effects of both estrogen and progesterone on the uterine muscle of both animals and man, but this information has not resulted in any truly rational method of treating premature labor. Lutrexin, since it contains an active principle which relaxes the uterus, should be available for the treatment of premature labor and should continue to be available until such time as a fully rational and effective treatment has been discovered.

I can say with complete candor, that the effectiveness as judged by clinical trials of Lutrexin in the treatment of dysmenorrhea, threatened abortion and premature labor is as well established as other agents, i.e., delalutin, progesterone, stilbestrol or multivitamins.

The problem resolves itself into two direct questions:

1. Does the FDA have the right to exclude a harmless remedy which may be "possibly effective"?

2. Should the FDA exclude a harmless remedy with biological potency just because the NRC panel noted, in its wisdom, that the product was "possibly effective"?

I personally believe that the FDA should not exclude Lutrexin even though it may have the power to do so.

Sincerely yours,

WILLARD M. ALLEN, M.D.,
Professor and Chairman,
Department of Obstetrics and Gynecology.

WMA:en

15 June 1970.

I hereby certify that the above is a Xerox copy of a letter which I mailed to Mr. Dunning on Dec. 10, 1969. I also certify that this letter was written by myself.

WILLARD M. ALLEN, M.D.
(S) Willard M. Allen, M.D.
State of Missouri, City of St. Louis.

Subscribed and sworn before me this 15th day of June, 1970.

(S) PATRICIA K. TILLEY,
Notary Public.

PROFESSIONAL STATISTICS

ALLEN, Dr. WILLARD M., Professor and Chairman, Department of Obstetrics and Gynecology, Washington University School of Medicine.

Year of Birth: 1904.

Medical Education: M.D., 1932 University of Rochester School of Medicine and Dentistry.

Year of License: 1940.

American Specialty Board: American Board of Obstetrics and Gynecology.

Primary Speciality: Obstetrics and Gynecology.

Societies:

American Association of Obstetrics and Gynecologists.
American Gynecological Society.
American College of Obstetricians and Gynecologists.
American College of Surgeons.
The Endocrine Society.

American Radium Society.
American Medical Association.

Miscellaneous:

Professor and Chairman, Department of Obstetrics and Gynecology, Washington School of Medicine, 1940—
Member of Panel on Drugs Used in Disturbances of the Reproductive System of the National Academy of Sciences-National Research Council.

Affidavit of Sylvester W. Trythall, M.D. in Support of Plaintiff's Memorandum in Opposition to Defendants' Motion To Dismiss and in the Alternative for Summary Judgment

STATE OF MICHIGAN,
County of Wayne, ss:

Sylvester W. Trythall, being first duly sworn, deposes and says:

1. I make this affidavit in support of plaintiff's Memorandum in Opposition to Defendants' Motion to Dismiss and in the Alternative for Summary Judgment, filed herewith in the above captioned cause.

2. I received an M.D. degree from University of Michigan School of Medicine in 1932, and was licensed to practice medicine in Michigan in 1932. My primary specialty is obstetrics and gynecology and I am certified by the American Board of Obstetrics and Gynecology, and am a fellow of the American College of Obstetricians and Gynecologists, as well as the American College of Surgeons, the American College of Obstetricians and Gynecologists, American Infertility Society and the International Infertility Society. I am affiliated with Crittenden General Hospital in Detroit, Michigan. My academic and administrative posts have been as follows:

Senior Attending Gynecologist
Chief of OB/GYN

3. I have engaged in the active practice of obstetrics and gynecology for approximately 37 years, and estimate that I have delivered or been associated in the delivery of over 10,000 babies. For the past 25 years I have been particularly practicing in the area of infertility and premature labor and threatened

and habitual abortion. I have used Lutrexin in the treatment of cases of threatened and habitual abortion, and premature labor for more than 15 years. During that time I have administered Lutrexin to a large number of women to prevent premature delivery of the infant. I have done a number of well-controlled studies in this area and a number of my published studies is attached hereto, made a part hereof and marked "Schedule A". In all of these studies I used Lutrexin as mentioned therein, and have found it to be a safe and effective drug.

4. From my extensive training and experience with clinical investigators and clinical investigations of drug and disease situations, as well as my own clinical studies, I am of the opinion that—

a) There are case situations in which double-blind or any type of placebo methods of clinical investigation may be unethical, immoral and even illegal;

b) cases involving threatened and habitual abortion and premature labor are such types of case situations;

c) in such cases, studies made by competent clinical investigators based on statistics, and historical control (including patient's own history) would be expected to produce "well controlled" results under the circumstances.

5. I am advised that the report of the panel of the National Academy of Sciences-National Research Council found Lutrexin to be "possibly effective" in the treatment of threatened abortion and premature labor, and understand that the Food and Drug Administration has moved to take Lutrexin off the market based upon this "possibly effective" evaluation, which the FDA has, without proper scientific evidence, expanded into an "ineffective" situation. In addition, I have reviewed the data of Hynson, Westcott and Dunning prepared by Drs. Gratton, Rezek, Majewski and Gray.

6. It is my opinion, based upon my experience with Lutrexin, indicated above, that Lutrexin is effective in the treatment of cases of threatened abortion and premature labor. I have found, in my practice, that it (together with cervical suture in some instances) is the most effective therapeutic agent for these indications. I have now under my care five selected pregnant women with a history of premature labor and one or more abortions due thereto. I have all of these women on regular doses of Lutrexin and furthermore, I do not believe I

could successfully practice in the aforementioned area of therapeutics if I did not have Lutrexin available. The safety of Lutrexin, not only in the dosage suggested in the drug's labeling but in amounts substantially in excess thereof, is beyond dispute; and I have never encountered any adverse effects in either mother or infant. Removal of Lutrexin from the OB/GYN's armamentarium would in my opinion border on the reprehensible, for, it would leave a currently unfillable void therein.

7. I am advised that Dr. Willard M. Allen, Professor and Chairman of the Department of Obstetrics and Gynecology in the School of Medicine of Washington University in St. Louis, Missouri, was a member of the N. R. C. panel which found Lutrexin "possibly effective". I consider Dr. Allen to be one of the foremost experts in OB/GYN in the country today.

8. I have also examined a letter of Dr. Allen's which, I am advised, has been filed with the Commissioner, Charles Edwards, M. D. of the Food & Drug Administration (Department of H. E. W.), and after appropriate oaths and acknowledgement by a Notary Public has been filed with the Clerk of the Court in this cause. In this letter and affidavit Dr. Allen states, among other things, as follows:

> Lutrexin contains a biologically active component (as yet unidentified structurally) which has a relaxing effect on the uterus of the laboratory animals and women. The NRC panel considered Lutrexin as possibly effective. This opinion of the panel does not mean that Lutrexin may possibly contain an active component. It means, on the contrary, that Lutrexin may be possibly effective in the conditions for which it is recommended, i.e., dysmenorrhea, threatened abortion or premature labor. The situation today is much the same, however, as 30 years ago in that the FDA seems to be interpreting "possibly effective" as ineffective and, once more, clinical evidence becomes of paramount importance.
>
> The clinical evidence which you have submitted, and which I have read carefully, does indicate that Lutrexin is beneficial in the three conditions for which it is recommended. The evidence also indicates that Lutrexin is not harmful or dangerous either to the patient or to

the fetus. You have submitted no evidence that Lutrexin is ineffective, nor do I know of any evidence in the medical literature indicating that it is ineffective. Lutrexin is recommended, for example. in premature labor. Uterine contractility is essential for delivery of the child but when uterine contractility comes prematurely the child may be lost from prematurity. Women have been forced to face the tragedy of premature labor for centuries because medical science has not provided as yet a complete explanation for premature labor, nor has medical science provided a scientifically rational method for preventing premature labor, or for stopping premature labor once it has started * * *.

I can say with complete candor, that the effectiveness as judged by clinical trials of Lutrexin in the treatment of dysmenorrhea, threatened abortion and premature labor is as well established as other agents, i.e., delalutin, progesterone, stilbestrol or multi-vitamins * * *.

I personally believe that the FDA should not exclude Lutrexin even though it may have the power to do so.

I wholeheartedly agree with Dr. Allen's statements concerning Lutrexin.

9. Based upon my experience, communications with OB/GYN practitioners in Detroit, Michigan and elsewhere, and upon my knowledge of the literature, it is my opinion that Lutrexin is generally recognized by OB/GYN physicians as both safe and effective in treatment of threatened abortion and premature labor. At the present time I have four patients on Lutrexin routine for RX of habitual late abortion.

10. I am prepared to testify as to these matters, and to present data to support the opinions expressed above, in a proceeding in court or before the Food and Drug Administration.

(S) S. W. Trythall, M.D.
SYLVESTER W. TRYTHALL.

Subscribed and sworn to before me this 14th day of September, 1970.

(S) ROSEMARY SCOTT,
Notary Public, Wayne County, Michigan.

PROFESSIONAL STATISTICS

AMA X
DO ———
ADA ——
AVMA ——

DR. SYLVESTER W. TRYTHALL, 20905 Green Field Road, Southfield, Michigan 48075.
Year of Birth: 1903.
Medical Education: University of Michigan Medical School, Ann Arbor M.D. Degree in 1932.
Year of License: 1935.
American Specialty Board: American Board of Obstetrics and Gynecology.
Primary Specialty: Obstetrics and Gynecology.
Type of Practice: Full time general practice or Other full time specialty practice.
Special Societies:
American College of Surgeons.
American College of Obstetricians and Gynecologists.
Date: June 14, 1968.

Affidavit of Fred B. Gray, M.D. in Support of Plaintiff's Memorandum in Opposition to Defendant's Motion To Dismiss and in the Alternative for Summary Judgment

STATE OF MICHIGAN,
County of Kent, ss:

Fred B. Gray, being first duly sworn, deposes and says:

1. I make this affidavit in support of plaintiff's memorandum in Opposition to Defendants' Motion to Dismiss and in the Alternative for Summary Judgment, filed herewith in the above captioned cause.

2. I received an M. D. degree from Vanderbilt University School of Medicine in 1940, and was licensed to practice medicine in Michigan in 1945. My primary specialty is obstetrics and gynecology and I am certified by the American Board of Obstetrics and Gynecology, and am a fellow of the American College of Obstetricians and Gynecologists, as well as the American College of Surgeons and the American College of

Obstetricians and Gynecologists. I am affiliated with both Butterworth and Blodgett Hospitals in Grand Rapids, Michigan.

3. I have engaged in the active practice of obstetrics and gynecology for approximately 25 years, and estimate that I have delivered approximately 7,000 babies. I have used Lutrexin in the treatment of cases of threatened and habitual abortion and premature labor for more than 12 years. During that time I have administered Lutrexin to a large number of women to prevent premature delivery of the infant, and have made what I believe to be a well-controlled study of 15 selected cases, a copy of which study is attached hereto, made a part hereof and marked Exhibit 1.

4. From my extensive training and experience with clinical investigators and clinical investigations of drug and disease situations, I am of the opinion that—

a) there are case situations in which double-blind or any type of placebo methods of clinical investigation may be unethical, immoral and even illegal;

b) cases involving threatened and habitual abortion and premature labor may well be such types of case situations;

c) in such cases studies made by competent clinical investigators based on statistics, or historical control (including patient's own history) may well be expected to produce "well controlled" results under the circumstances.

5. I am advised that the report of the panel of the National Academy of Sciences-National Research Council found Lutrexin to be "possibly effective" in the treatment of threatened abortion and premature labor, and understand that the Food and Drug Administration has moved to take Lutrexin off the market based upon this "possibly effective" evaluation. In addition, I have reviewed the data of Hynson, Westcott and Dunning submitted to FDA in response to the panel's report.

6. It is my opinion, based upon my experience with Lutrexin, indicated above, that Lutrexin is effective in the treatment of cases of threatened abortion and premature labor. I have found, in my practice, that it is the most effective therapeutic agent for these indications. The safety of Lutrexin, not only in the dosage suggested in the drug's labeling but in amounts substantially in excess thereof, is beyond dispute; and I have never

encountered any adverse effects in either mother or infant. Removal of Lutrexin from the OB/GYN's armamentarium would in my opinion border on the reprehensible, for, it would leave a currently unfillable void therein.

7. I am advised that Dr. Willard M. Allen, Professor and Chairman of the Department of Obstetrics and Gynecology in the School of Medicine of Washington University in St. Louis, Missouri, was a member of the N. R. C. panel which found Lutrexin "possibly effective". I consider Dr. Allen to be one of the foremost experts in OB/GYN in the country today.

8. I have also examined a letter of Dr. Allen's which, I am advised, has been filed with the Commissioner, Charles Edwards, M. D. of the Food & Drug Administration (Department of H. E. W.). In this letter Dr. Allen states, among other things, as follows:

> Lutrexin contains a biologically active component (as yet unidentified structurally) which has a relaxing effect on the uterus of the laboratory animals and women. The NRC panel considered Lutrexin as possibly effective. This opinion of the panel does not mean that Lutrexin may possibly contain an active component. It means, on the contrary, that Lutrexin may be possibly effective in the conditions for which it is recommended, i.e., dysmenorrhea, threatened abortion or premature labor. The situation today is much the same, however, as 30 years ago in that the FDA seems to be interpreting "possibly effective" as ineffective and, once more, clinical evidence becomes of paramount importance.
>
> The clinical evidence which you have submitted, and which I have read carefully, does indicate that Lutrexin is beneficial in the three conditions for which it is recommended. The evidence also indicates that Lutrexin is not harmful or dangerous either to the patient or to the fetus. You have submitted no evidence that Lutrexin is ineffective, nor do I know of any evidence in the medical literature indicating that it is ineffective. Lutrexin is recommended, for example, in premature labor. Uterine contractility is essential for delivery of the child but when uterine contractility comes prematurely the child may be lost from prematurity. Women have been forced to face the tragedy of premature labor for centuries

because medical science has not provided as yet a complete explanation for premature labor, nor has medical science provided a scientifically rational method for preventing premature labor, or for stopping premature labor once it has started * * *.

I can say with complete candor, that the effectiveness as judged by clinical trials of Lutrexin in the treatment of dysmenorrhea, threatened abortion and premature labor is as well established as other agents, i.e., delalutin, progresterone, stilbestrol or multivitamins * * *.

I personally believe that the FDA should not exclude Lutrexin even though it may have the power to do so.

I wholeheartedly agree with Dr. Allen's statements concerning Lutrexin.

9. Based upon my experience, communications with OB/GYN practitioners in Grand Rapids, Michigan and elsewhere, and upon my knowledge of the literature, it is my opinion that Lutrexin is generally recognized by OB/GYN physicians as both safe and effective in treatment of threatened abortion and premature labor.

10. I am prepared to testify as to these matters, and to present data to support the opinions expressed above, in a proceeding in court or before the Food and Drug Administration.

(S) Fred B. Gray, M.D.
FRED B. GRAY, M.D.

Subscribed and sworn to before me this 6th day of March, 1970.

(S) GORDON J. DUPREY,
Notary Public, Kent County, Michigan,
My Commission Expires: Feb. 6, 1973.

AMA Directory—AM Directory OB/GYN

PROFESSIONAL STATISTICS

DR. FRED B. GRAY,
456 Cherry Street, S.E.,
Grand Rapids, Michigan 49503.
Year of Birth: 1912.
Medical Education: Vanderbilt University School of Medicine, Nashville, Tennessee, M.D. Degree in 1940.

Year of License: 1945.
Amer. Specialty Board: American Board of Obstetrics and Gynecology.
Primary Specialty: Obstetrics and Gynecology.
Type of Practice: Full time specialty practice.
Internship and Residence:
Butterworth Hospital, July 1940–41.
Vanderbilt Hospital, 1941–42.
Butterworth Hospital, 1945–47.
Hospital Affiliation:
Butterworth Hospital, Senior.
Blodgett Hospital (Visiting).
Membership:
Fellow American College of Surg.
KCMS.
American Medical Association.
American College of Obstetricians and Gynecologists.
November 1968.

Affidavit of Joseph F. Sadusk, Jr., M.D. in Support of Plaintiff's Memorandum in Opposition to Defendants' Motion To Dismiss and in the Alternative for Summary Judgment

STATE OF MICHIGAN,
County of Wayne, ss:

Joseph F. Sadusk, Jr., being duly sworn, deposes and says:

1. I make this affidavit in support of plaintiff's Memorandum in Opposition to Defendant's Motion to Dismiss and in the Alternative for Summary Judgment, filed herewith in in the above-captioned cause.

2. I am a physician, currently Vice President for Medical and Scientific Affairs of Parke, Davis & Company, manufacturer of pharmaceuticals and allied products; formerly Professor of Medicine and Associate Dean of the School of Medicine of Johns Hopkins University; formerly Director of the Bureau of Medicine and Medical Director, Food & Drug Administra-

tion, U.S. Department of Health, Education and Welfare; and a more detailed curriculum vita and List of Publications are attached hereto, made a part hereof and marked Exhibits A and B.

3. That I made a speech on October 8, 1964 to the American College of Physicians which was presented in the Bulletin of the American College of Physicians in the November-December 1964 issue, at which time I was Director of the Bureau of Medicine and Medical Director of the FDA. (A true copy of which is attached hereto and made a part hereof, and marked Exhibit C). Said speech was approved by the Office of the Commissioner, FDA, and may be said to be in accord with FDA policies.

4. That I am still of the same opinion expressed therein concerning "well controlled" clinical studies.

5. From my extensive training and experience in clinical investigations of drug and disease situations I am of the opinion that—

a) there are case situations in which double-blind or any type of placebo methods of clinical investigation may be unethical, immoral and even illegal;

b) cases involving threatened and habitual abortions and premature labor may well be such types of case situations;

c) in such cases studies made by competent clinical investigators based on statistics, or historical controls (including patient's own history) may well be expected to produce "well controlled" results under the circumstances.

6. That I am prepared to testify in open court as to the foregoing matters.

(S) Joseph F. Sadusk, Jr.
JOSEPH F. SADUSK, Jr.,

Subscribed and sworn to before me, a Notary Public in and for the County of Wayne and State of Michigan, on this 22nd day of January, 1970.

(S) RINA J. BABUSCI,
Notary Public,
Wayne County, Michigan,
My Commission Expires: 10-26-73.

[Exhibit A]

Curriculum Vitae

Joseph Francis Sadusk, Jr., A.B., MD.
Vice President, Medical and Scientific Affairs,
Parke, Davis & Company.

Born October 4, 1909, Baltimore, Maryland.

Degrees and Fellowships:

1927–29—Loyola College (Baltimore).
1929–31—A.B., Johns Hopkins University.
1931–35—M.D., Johns Hopkins University.
1933–35—Henry Strong Denison Fellow in Physiological Chemistry.

House Officeship Training:

1935–36—Resident House Officer in Medicine, Johns Hopkins Hospital.
1936–37—Resident House Officer in Obstetrics, Johns Hopkins Hospital.
1937–38—Asst. Resident in Medicine, New Haven Hospital.
1938–39—Asst. Resident in Obstetrics, Johns Hopkins Hospital.
1939–40—Resident in Medicine, New Haven Hospital.

Faculty Positions:

1937–38—Assistant in Medicine, Yale Univ. Medical School.
1938–42—Instructor in Medicine, Yale Univ. Medical School.
1946–47—Asst. Professor of Medicine, Yale Univ. Medical School.
1947–48—Clinical Instructor in Medicine, New York University College of Medicine.
1948–49—Adjunct Clinical Professor of Medicine, George Washington University School of Medicine.
1949–58—Asst. Clinical Professor of Medicine, Stanford Medical School.
1958–62—Assoc. Clinical Professor of Medicine, Stanford Medical School.
1962–64—Professor and Chairman, Department of Preventive Medicine and Community Health, George Washington University School of Medicine.

1962–64—Director of University Clinics, George Washington University Hospital.
1962–66—Professor of Preventive Medicine and Community Health, George Washington University.
1966–67—Professor of Medicine, Johns Hopkins University.
1966–67—Associate Dean for Community Medicine, The Johns Hopkins University School of Medicine.
1967– —Adjunct Professor of Medicine, Wayne State University School of Medicine.

Hospital Appointments:

1940–42 and 1946–47—Associate Visiting Physician, New Haven Hospital.
1947–48—Assistant Visiting Physician, Bellevue Hospital (New York).
1948–49—Associate Visiting Physician, George Washington University and Gallinger Hospitals (Washington, D.C.)
1949–62—Visiting Physician, Stanford-Lane Hospital and Stanford University Hospital (San Francisco-Palo Alto)
1959–62—Staff Physician, Presbyterian Medical Center (San Francisco)
1949–62—Staff Physician, Peralta, Providence and Merrit Hospitals (Oakland)
1958–59—President, Peralta Hospital Medical Staff
1957–62—Member, Board of Trustees, Peralta Hospital
1957–62—Member, Medical Advisory Board, Peralta Hospital
1962–66—Staff Physician, George Washington University Hospital
1963–66—Consultant in Infectious Disease, District of Columbia Children's Hospital
1963–66—Consulting Staff, Washington Hospital Center
1966–67—Physician, Johns Hopkins Hospital
1967– —Senior Associate Attending Physician, Detroit General Hospital

Consultants Positions:

1941–42—Consultant to Secretary of War.
1941–42—Member, Commission on Pneumonia, U.S. Army Epidemiological Board.
1946–47—Consultant to Secretary of War.

1946–47—Member, Commission on Viral and Rickettsial Diseases, U.S. Army Epidemiological Board.
1946–48—Consultant in Tropical Medicine to U.S. Army Research and Post Graduate School.
1946–47—Consultant in Internal Medicine, Laurel Heights Sanitarium, Shelton, Connecticut.
1949–52—Consulant to Secretary of Defense.
1949–52—Consultant in Infectious Diseases, Oakland, VA Hospital.
1955–61—Area Consultant to Veterans Administration in Tropical Medicine.
1955–61—Consultant in Tropical Medicine, San Francisco, V.A. Hospital.
1958–62—Chairman, Medical Advisory Committee, Oakland V.A. Hospital.
1961–64—Member, Civilian Health and Medical Advisory Council (Asst. Secretary of Defense for Manpower).
1962–64—Executive Reserve (Secretary of Defense—United States Government.

Government Positions:

U.S. Army—1942–46—Captain to Colonel, Medical Corps—

1. Faculty, Army Medical School (Dept. Bacteriology and School of Tropical Medicine)—1942.
2. Staff, Hawaiian Department (Spec. Assignment by Secretary of War)—1942–43.
3. Executive Officer, Special Mission on Scrub Typhus, U.S. Army—1943.
4. United States of America Typhus Commission Executive Officer—1943–46.

Department of Defense—

Executive Director, Committee on Medical Sciences, Research and Development Board, Secretary of Defense—1948–49.

Department of Health, Education and Welfare

Medical Director, Food and Drug Administration—1964–66.

Other Administrative:

1947–48—Associate Medical Director, Prudential Insurance Company.

1967–68—Vice President, Medical Affairs; Parke, Davis & Company.

1968–Present—Vice President, Medical and Scientific Affairs; Parke, Davis & Company.

1968–Present—Member of the Board of Directors; Parke, Davis & Company.

1969—Member, Board of Trustees, St. Johns Hospital, Detroit, and Chairman of Planning Committee.

1969—Member, Board of Trustees, Lindenwood College II.

Awards and Decorations:

Legion of Merit and Oak Leaf Cluster—1943 and 1954.

U.S.A. Typhus Commission Medical—1964.

Fourth Annual Roland T. Lakey Lecture Award, The Rho Chi Pharmaceutical Honor Society, Wayne State University College Pharmacy—1967.

Honorary Member, American Medical Society of Vienna (Austria)—1969.

Medical Society Committee Appointments:

1950–55—Chairman, Committee on Medical Practice, Alameda-Contra Costa County Medical Association.

1954–58—Chairman, Medical Review and Advisory Board, California Medical Association.

1956–66—Member, and Chairman (1962–66), Committee on Medicolegal Problems, American Medical Association.

1957–59—Chairman, American Medical Association-American Hospital Association Committee on Medicolegal Education.

1960–69—Member, American Medical Association Liaison Committee with American Bar Association.

1958–66—Member, Committee on Insurance, American College of Physicians.

1960–66—Member, Board of Trustees, American College of Physicians Group Life Insurance Plan.

1950–62—Various other Committees of Alameda-Contra Costa Medical Association.

1963–65—Member, Committee on Medicolegal Education, Medical Society of the District of Columbia; Consultant—1965–66.

1967–68—Member, Committee on Social Policy for Medical Care, New York Academy of Medicine.

1967—President—Pharmaceutical Manufacturers Association Foundation Advisory Committee on the Faculty Development Awards.

1967–Present—Committee on Medicine and Pediatrics (The Society of Medical Consultants to the Armed Forces).

Medical Society Membership:

Fellow of American College of Physicians.

American Society for Clinical Investigation.

American Federation for Clinical Research.

American Society of Tropical Medicine.

American Medical Association and other state and county Medical Societies (Connecticut, New Jersey, California, Maryland, Michigan and District of Columbia).

American Society of Internal Medicine.

California Society of Internal Medicine (President 1961–62); Honorary Life Member (1962–Present).

Tropical Medicine Association of Washington, D.C.

Academy of Medicine of Washington, D.C.

Society of Medical Consultants to the Armed Forces.

Michigan Society of Internal Medicine.

American Public Health Association.

American Society of Tropical Medicine and Hygiene.

American Therapeutic Society.

Internal Medicine:

1944– —Certified by American Board of Internal Medicine.

1949–62—Practice of Internal Medicine, Oakland, California.

States Licensed to Practice: California, Connecticut, District of Columbia, Maryland, Michigan, New Jersey, New York.

Clubs:

The 100 Club (Oakland, 1953–64) (President 1960–61).

Cosmos Club (Washington, D.C.), 1962–President.

The Hundred Club of Detroit, 1967– .

The Detroit Club, 1967– .

Detroit Athletic Club, 1967– .

Grosse Pointe Club, 1968– .

Publications:

Publications in medical journals and contributor to medical textbooks in the field of biochemistry, infectious diseases, chemotherapy, anti-syphilitic therapy, viral and rickettsial diseases, medicolegal problems, regulation of drugs, and biomedical science communications.

[Exhibit C]

(Vol. 5, No. 6 November-December, 1964)

THE BULLETIN OF THE AMERICAN COLLEGE OF PHYSICIANS

THE DEFINITION OF THE EFFICACY OF A DRUG UNDER THE LAW

JOSEPH F. SADUSK, JR., F.A.C.P., Medical Director, Food and Drug Administration, U. S. Department of Health, Education, and Welfare.

In 1912, an amendment to the Food and Drug Act of 1906 established the first Federal authority to act against drugs that were labeled with false and fraudulent claims for therapeutic effectiveness. However, such false claims made "out of ignorance" could not be attacked under this amendment, in other words, the burden of proof was on the Government to prove fraud on the part of the manufacturer.

The Elixir of Sulfanilamide disaster led to the new drug provisions of the Federal Food, Drug, and Cosmetic Act of 1938. While basic provisions in this Act required a manufacturer to establish safety of a drug before it could be marketed, the Food and Drug Administration had to permit the marketing of such a new drug when an application showed it to be safe, even though evidence of effectiveness was lacking. Nevertheless, the Food and Drug Administration did have limited authority under these 1938 provisions to deal with effectiveness through its power to rule in safety, since many drugs are capable of causing serious adverse effects; and it was a common sense conclusion that a safety decision could be reached only on the basis that the potential benefits of a drug outweighed the risk involved in its use.

Presented in a Symposium on Drug Investigation and Therapy, at the Second Fall Meeting of the American College of Physicians, Los Angeles, California, October 8, 1964.

The Kefauver-Harris Amendments of 1962 revised the definition of a new drug to say that a new drug is one which by reason of its composition is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." As a result of these amendments, a new drug application can now be rejected not only when there is insufficient evidence to establish its safety, but also if there is a lack of substantial evidence to show that the drug will have the effect it purports or is represented to have under conditions of use recommended in the proposed labeling.

Let us define several terms. The word *labeling* includes the contents of the package circular which the manufacturer is required to enclose with the bottle of medication. This circular may vary from several hundred to a thousand or more words and briefly, but very specifically, presents the trade name, generic name, chemistry, pharmacology, clinical indications, precautions, side effects, contraindications, routes, methods, and dosage. Much effort is expended by the manufacturer and the Food and Drug Administration on this labeling which represents a full summary of knowledge of chemists, pharmacologists, investigators, and clinicians. Under the present conditions of distribution of this package circular, it does not get to the physician as effectively as we should like; though it is generally true that with a very modest effort the physician may obtain it from his pharmacist or examine it from a physician's sample package that comes to his desk. In addition, not only does the 1962 Amendment require the drug manufacturer to furnish a copy of the Food and Drug Administration approved package circular for a new drug to the physician upon request, but all other promotional material for drugs, including advertisements, are required to contain summaries drawn from the package brochure. Nevertheless, the Food and Drug Administration is giving serious consideration to better methods of distribution of present package insert information to physicians and other practitioners, hospitals, and pharmacists.

As used in the law, the term *"substantial evidence"* is defined to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts

qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use" as recommended in the proposed labeling.

Let us inquire into this definition of efficacy as expressed in the law. We need to discuss further and in such detail as time permits the following phrases:

1. Adequate and Well-Controlled Investigations.
2. Experts Qualified by Scientific Training and Experience.
3. On the Basis of Which It Can Fairly and Responsibly be Concluded That the Drug Will Have Its Claimed Effect.

The three parts of this definition arose out of the Congress' belief, based on the Kefauver investigations, that too many drugs were being promoted on the strength of random observations by physicians of no special competence in drug investigation, thus producing a type of evidence of essentially the testimonial or other poorly controlled character. No really responsible group of medical experts could accept this sort of evidence as a basis for approval of medical claims.

In final analysis, what was intended here was to require the development of the kind of scientific evidence that would enable an expert group, such as consultants selected by the Council on Drugs of the American Medical Association to review a particular drug, to come to a conclusion that the drug could reasonably be expected to perform in the clinical practice for which it was intended in the way that the labeling said it would.

Let us take the three parts one by one.

1. Adequate and Well-Controlled Investigations

Obviously, many experimental factors must be controlled and, in general, the effect on the disease process in patients receiving the drug needs to be compared with patients with similar disease conditions who do not receive the drug. This is preferably done by placebo comparisons in well-designed double-blind clinical studies.

But this is not the only type of study that can be called well-controlled. Sometimes such studies are not ethically permissible or, for practical reasons, are not feasible. Here the design of the study, the competence and experience of the investigator, and the adequacy of the observations and laboratory and other test procedures that are employed to record and weigh the clinical effects of the drug take on paramount importance. With some drugs intended for use in disease states, the natural histories of which are reasonably well understood and in which the pharmacological behavior of the drug can be observed by objective measurements, the blind and double-blind studies take on less significance. And even in states where there are little or no objective measures of patient response, careful planning coupled with systematic observation and accurate recording of the patient's course may qualify as a well-controlled study. The use of other disciplines such as statistics may provide the extra support to make the study an acceptable and convincing one.

2. Experts Qualified by Scientific Training and Experience

And now let us address ourselves to a discussion of the part of the law which defines an expert investigator—"experts qualified by scientific training and experience." Here we are faced with the need of determining the quality of the investigator who furnishes the evidence upon which the efficacy and safety of a drug is determined. Since the scientific community has not specifically defined or described those criteria which establish the competency of an investigator, it does not seem likely that a Governmental agency will ever be able to establish such standards. It is clear that the Food and Drug Administration will have to approach this task as any scientific administrator does—to consider each investigator on the merits of his curriculum vitae, his past record of accomplishment, the scientific environment in which he is doing the investigation, and the nature and quality of the recorded observations. Certainly, it does not seem likely that the Food and Drug Administration will ever publish a list of so-called "qualified" investigators.

We have heard stated that only physicians in the course of their practice can determine the effectiveness of drugs and what

drug to employ in a particular patient. The law does not interfere with these ideas insofar as the use of a drug is concerned for that doctor's patient, but it does prevent the marketing of a new drug with labeling and advertising making unsupported therapeutic claims.

It is common knowledge that the pharmaceutical industry is faced with a significant issue in the shortage of qualified investigators. Drugs are becoming more and more complex and the use of the general doctor, without specific experience in clinical investigation, in testing drugs in his office in the midst of a busy practice is probably coming to an end. The need for training of physicians in the drug research field has reached a critical stage, and this problem must be met by the joint efforts of government, industry, and the scientific community.

3. On the Basic of Which It Can Fairly and Responsibly be Concluded That the Drug Will Have Its Claimed Effect

The third and most important part of the definition of "substantial evidence" requires that it provide a basis on which a properly qualified expert can fairly and responsibly conclude that the drug will have effectiveness claimed for it.

Neither legally nor medically is there any requirement that all investigators show effectiveness of the drug being studied. Nor is there a requirement that any fixed number of investigations be made, or a fixed number of investigators used, or indeed that the drug under study be found more effective than other drugs for the same purpose.

Since medical investigation cannot always be an exact science the law does not require that the evidence demonstrate effectiveness beyond peradventure.

What is required is a body of scientific data drawn from the investigations that will be convincing to those responsible for the decision to approve or not to approve the marketing of the drug. It must be assumed that these responsible officials have the qualifications to make an evaluation of the data. If they do not, they must draw upon the scientific community for the resource people who do. Here we expect to obtain assistance from our Advisory Committees and Panels which presently are in the planning state in the Bureau of Medicine. Here we expect

to bring in a substantial number of consultants from the scientific community to advise us on decisions and to prepare guidelines for review.

But no panel and no consultant can help us unless provided with the kind of data that they are entitled to expect as a foundation for *responsible* decision. We cannot ask these experts to act on testimonials or random observations. We will not act on them ourselves.

What we want, and what the law requires, is data that would enable the appropriately qualified experts to say responsibly whether or not the drug may be expected to perform as it is represented. This kind of evidence is not hard for the qualified person to recognize when he sees it.

You are doubtless aware of the difference of opinion which exists between the Food and Drug Administration and Industry as to the requirements for efficacy testing of drugs manufactured and approved prior to 1962. The Food and Drug Administration holds that the effectiveness provisions of the Kefauver-Harris Amendments apply not only to the approval of new drug applications received after enactment of the 1962 Amendments, but that after October 9, 1964 these provisions will also apply to all drugs for which new drug applications were cleared since 1938. However, the Pharmaceutical Manufacturers Association and a number of its member firms have filed suit in the Federal Court at Wilmington, Delaware in an effort to establish that the Food and Drug Administration does not have authority to require reports for drugs cleared through the new drug procedures in previous years, but which the Industry now regards as "no longer new drugs."

The results of that litigation may have a very important bearing on whether the Food and Drug Administration may apply these new effectiveness provisions to many drugs now on the market. At issue is the question of whether the drug manufacturer must offer substantial evidence that the drug he is marketing is effective for the purposes claimed in its labeling; or whether he is entitled to continue to market it unless the Food and Drug Administration develops adequate evidence to assume the burden of proof in court that the drug is ineffective for the purposes claimed. This issue is of major concern to the medical profession as well as to the public generally and drug

manufacturers. The outcome will be of critical importance in determining whether the Food and Drug Administration can assure the effectiveness of the Nation's drug supply.

Whether or not the issue is to be resolved in favor of the Food and Drug Administration, the task of reevaluating the effectiveness of drugs now on the market must be accomplished. On the one hand it would be on the basis of these new provisions of the law; on the other hand it would be under the old law requiring case by case litigation in the courts. In either event, years of effort may be required even with the fullest cooperation of the medical community and the pharmaceutical industry.

Realizing the long and difficult task ahead for the Bureau of Medicine, the Commissioner presented a list of certain categories of drugs to the Subcommittee on Reorganization and Internal Organization of the Senate Committee on Government Operations on May 28, 1964, for priority review. He has very recently accepted from the Bureau of Medicine a list of these thirteen categories of drugs in order of priority for the Bureau to apply its initial review efforts:

1. Proteolytic enzymes (oral and injectable).
2. Progestational agents.
3. Drugs offered for anxiety and apprehensive states, most tranquilizers, monoamine oxidase inhibitors.
4. Non-prescription iron preparations.
5. Pediatric dosages.
6. Topical ophthalmic antibiotic combinations.
7. A number of sustained-release drugs.
8. Other topical antibiotic combination products.
9. Bioflavonoids.
10. Hormone creams.
11. Drugs used in pregnancy.
12. Topical antihistamines.
13. Topical 'caines (local anesthetics).

It must be realized that this order of priority may change with time and indeed certain specific drugs, or even categories of drugs, may be deemed in the future to be of higher priority than those listed.

In closing, we trust you realize that the law now provides an instrumentality for the Scientific Community, the Pharmaceu-

tical Industry, and the Food and Drug Administration to join and coordinate their efforts to reasonably assure our Nation that everything possible has been done in the light of scientific knowledge to promote the safety, effectiveness, and reliability of the country's drug supply.

36 FR. 11763 (June 18, 1971)

FOOD AND DRUG ADMINISTRATION

HYNSON, WESTCOTT & DUNNING, INC.

Notice of Withdrawal of Approval of New-Drug Applications

On March 22, 1969, there was published in the FEDERAL REGISTER (34 FR. 5556) a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new-drug applications for drugs containing lututrin on the ground that there is a lack of substantial evidence that lututrin has the effect or contributes to the effect which the drugs purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Hynson, Westcott & Dunning, Inc. Charles and Chase Streets, Baltimore, Mr. 21201, holder of NDA No. 8–986, Lutrexin tablets and NDA No. 10–144, Trexinest tablets by the October 16, 1970 letter of its counsel, has requested a hearing on the following issues:

> (1) Whether its lututrin drugs are exempt from the efficacy requirements of 21 U.S.C. 355 under section 107 (c) of Public Law 87–781; (2) whether its lututrin drugs are "new drugs" within the meaning of 21 U.S.C. 321(p) (1); and (3) whether there is a lack of substantial evidence of effectiveness to support the claims made for Lutrexin.

In support of its request for a hearing on the issue of substantial evidence of effectiveness, Hynson, Westcott, and Dunning, Inc. (hereinafter referred to as "HW&D") has submitted a list of its medical documentation previously filed with the Agency, including all data submitted in connection with NDA No. 10-

144, correspondence between HW&D officials and the Agency or other persons, labeling for the lututrin drugs, literature articles submitted to the National Academy of Science-National Research Council, and the HW&D letter of August 18, 1969, in which the company first elected to avail itself of the opportunity for hearing.

To support its hearing request on the contentions that HW&D's lututrin drugs are exempt from the efficacy requirements of 21 U.S.C. 355, the company has submitted copies of its pleadings, legal memorandum, exhibits, and affidavits, as well as the transcript and order in Hynson, Westcott and Dunning, Inc. v. Finch (C.A. No. 211112, D. Md., decided Sept. 11, 1970).

The Commissioner of Food and Drugs has reviewed HW&D's request for hearing and the medical documentation submitted, and makes the following findings:

1. The drugs, their rationale and claims

a. Lutrexin is labeled as containing 3,000 units of lututrin per tablet. Lututrin is claimed to be a porcine uterine relaxing hormone effective in the treatment of functional dysmenorrhea, selected cases of premature labor and threatened and habitual abortion. The package insert claims the drug has demonstrated activity on the living animal uterus, that it relaxes the contracted uterine muscle by direct action thereon, or by blocking pituitary action.

b. Trexinest is labeled as containing 500 units of lututrin and 1.0 milligrams of estrogen, in the form of sodium estrone sulfate, per tablet. Trexinest is recommended for the treatment of menopausal disorders. The package insert claims that the combination is more effective than lututrin or estrogen alone and points to lututrin as the responsible agent in the drug's effectiveness.

II. The applicable regulations

HW&D's contention that it has an unconditional right to a hearing is denied. The hearing regulations, 21 CFR 130.14, require that a person seeking a hearing set forth specific facts showing the existence of genuine and substantial fact issues which requires a hearing. The order of May 8, 1970 (35 F.R.

7250) granted persons involved in notices of hearing, including HW&D, 30 days in which to amend their requests for hearing to comply with the new regulations. The company was given actual notice on May 19, 1970, that it was required to comply with these regulations in order to properly avail itself of an opportunity for hearing. Applications of the regulations have been upheld by the courts. Pfizer, Inc. v. Richardson, 434 F. 2d 536 (C.A. 2, 1970); Upjohn Co. v. Finch, 422 F. 2d 944 (C.A. 6, 1970); Pharmaceutical Manufacturers Association v. Richardson, 318 F. Supp. 301 (D. Del., 1970). HW&D is bound by the judgment in the last case cited.

III. The Request for a Hearing

a. *The issues of exemption under section 107(c) of Public Law 87–781 and under 21 U.S.C. 321(p)(1).* The request for a hearing on these issues is denied. The new-drug applications involved had not been withdrawn prior to enactment of Public Law 87–781. They were "deemed approved" under the 1962 amendments to the Act and are subject to withdrawal on the basis of the effectiveness requirements of the amendments.

b. *Lutrexin and Trexinest are new drugs within the meaning of 21 U.S.C. 321(p)(1).* The conclusions of HW&D's affiants that these drugs are not new drugs cannot be accepted. No adequate and well-controlled clinical investigations published in the medical literature have been identified. Therefore, there is no data base upon which experts can fairly and responsibly conclude that the safety and effectiveness of the drugs has been proven and is so well established that the drugs can be generally recognized among such experts as safe and effective for their intended uses.

The affiants identify 11 studies as establishing the claims made for the drugs. None purports to be an adequate and well-controlled clinical investigation. They may be summarized as follows:

(1) Majewski and Jennings: Uterine Relaxing Factor for Premature Labor, Ob. & Gyn. 5:649–652 (May 1955); and Further Experiences with a Uterine Relaxing Hormone in Premature Labor, Ob. & Gyn. 9:322–325 (March 1957) by the same authors are one study. The first paper is a preliminary

study on 20 patients and the latter is the report on enlarged group of 88 patients. The authors acknowledge that results in the total group are less favorable than in the preliminary study, but conclude that the results are encouraging. Concomitant medication was given an unstated number of patients. There is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced. Nine patients out of 88 in whom the drug proved ineffective were excluded from the report for "statistical reasons". Six patients received the drug for less than 3 hours, which the authors without explanation considered too short a time for a true test of effectiveness. There is no summary or explanation of the statistical methods used in analysis of the data to show that results were not biased or due to chance.

(2) Majewski: Statistical Evaluation in The Reduction of the Incidence of Prematurity (1968) is unpublished. The author claims successful treatment in 86 percent of cases treated in his practice over a 10-year period. Substantiating documentation to establish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided. The author acknowledges that some patients with medical complications such as placenta praevia were included in the study. Lutrexin is not claimed to have value in the medical or obstetrical complications of pregnancy which occur in a significant percentage of premature births

The paring of live birth percentages by number of pregnancies before and after Lutrexin treatment such as in Table I are all inappropriate. For example, of the 24 cases with one previous pregnancy, 11 live births before treatment and 18 live births after treatment are compared. However, for each of the 18 live births after treatment, an additional pregnancy had elapsed so that the number of previous pregnancies associated with the number 18 is two, not one; as such, the number 18 should be compared with the number 16, the total live births for two previous pregnancies.

The data in Table I does not admit of statistical evaluation by the chi-square test since the test is based on the assumption that each number in the columns of Table I is the sum of independent yes or no responses, e.g., for the one patient with seven previous pregnancies, four live births are correlated, thus ignor-

ing the sample size of one and using an erroneous sample size of four.

(3) Rezek: The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luterum in the Treatment of Dysmenorrhea, Am. J. Ob. & Gyn. 66:396-402 (August 1953). The report does not state the method of patient selection, nor does it indicate comparability of pertinent variables such as severity or duration of diseases. Concomitant medication is not excluded. No explanations of the methods of observation, the recording of results, and steps taken to minimize patient and investigator bias are provided. The historical controls employed are inappropriate.

(4) Rezek: Lutrexin in the Treatment of Premature Labor, Ann. N.Y. Acad. Sci. 75:995–997 (January 1959). The method if selection of the patients does not show progressive dilation of the cervix, which is necessary to accurately diagnose premature labor. The methods of observation and the recording of results are not explained. No statistical evaluation was presented to show that results claimed are significant in terms of the patient population.

(5) Gratton: The Treatment of Infertility and Prematurity Pregnancy Problems (1968) is unpublished. Patients received numerous concomitant therapies until the fifth month of pregnancy which prevents scientific attribution of results to lututrin therapy. The method of patient selection is unexplained.

Statistically the study lacks adequate design and evaluation. There is no showing that the cases studied are representative of the population to which inferences are made. The pairings of live births percentages in Table II cannot be compared since the number of previous pregnancies differs between the pair percentages and there is no data on possible etiologic factors of previous abortions and premature labor.

(6) Gray: Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases (undated) is an unpublished report on 15 selected cases the author has treated. No plan or protocol is provided to allow determination of the objectives of the study, the method of patient selection, diagnostic criteria of the condition to be

treated, laboratory tests to be made, the methods of observation and recording of results. The author's review of his records does not constitute an adequate and well-controlled investigation.

(7) Four papers by Dr. Trythall were listed in the attachment to his affidavit. In only one article is lutrexin ever mentioned. The three sentences devoted to the drug provide no information whatsoever except that the author claims to have found it effective in his practice.

The affiants state that double blind investigations of lututrin are unethical because the drug is effective and complications of pregnancy may be life-threatening. The Commissioner does not reach that issue, since none of the historically controlled studies relied upon were adequate and well-controlled investigations.

There are other reasons why HW&D's medical data lack merit, but in view of the above finding their delineation is unnecessary.

c. *The issue of substantial evidence of effectiveness.* The request for a hearing on this ground is denied. The regulations, 21 CFR 130.14, require HW&D to submit a well organized and full factual analysis of the clinical and other investigational data it is prepared to prove at a hearing. The request must set forth specific facts showing that there is a genuine and substantial issue of fact requiring a hearing. HW&D has not attempted compliance with these requirements.

Rather than identify and discuss the efficacy data relied upon to support the claims made for its drugs, the company has merely provided a list, extending to four pages, of practically all materials ever submitted to the Agency and the NAS–NRC. The materials are described, for the most part, in general terms (e.g., "data submitted in connection with New Drug Application for Lutrexin tablets * * *, Lutrexin bibliography * * *, Trexinest bibliography * * *, reprints and abstracts * * *). What the Commissioner is required to do is to determine from this material, what HW&D may or may not consider relevant and, therefore, relies upon. In the case bibliographies, the Commissioner would be required to research each article and then determine if it is relevant, or whether HW&D might consider it

relevant. Because such a procedure is not contemplated by the regulation, the request for hearing is denied for failure to comply with applicable regulations.

Apart from the refusal of HW&D to comply with 21 CFR 130.14, the most basic material in the Lutrexin new-drug application reveals a lack of adequate and well-controlled investigations showing that lututrin will have the effect HW&D claims for it.

The only evidence submitted that lututrin may have biological activity in humans when taken orally is a test on nine women by Jones and Smith in which positive results were reported to have been obtained in six subjects. No plan or protocol was stated. No data on the participating patients was provided. No explanation of procedures for patient selection, or criteria for inclusion in the study, or appropriate laboratory tests before and after administration of lututrin was provided. No statistical analysis showing the test population was of significant size or that results obtained were significant is shown. Moreover, there is no evidence that results claimed have ever been reproduced in humans by other investigators.

Therefore, the Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1053, as amended; 21 U.S.C. 355(e)), and under the authority delegated to him (21 CFR 2.120), finds that on the basis of new information before him with respect to each of said drugs evaluated together with the evidence available to him when each application was approved, there is a lack of substantial evidence that each of the drugs will have the effects it is purported or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof.

Pursuant to the foregoing findings, approvals of the above new-drug applications, and all amendments and supplements thereto, are withdrawn effective on the date of the signature of this document.

Dated: May 31, 1971.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc. 71-8557 Filed 6-17-71; 8:46 a.m.]

Petition of Hynson, Westcott & Dunning, Incorporated For a Stay of the Order of the Commissioner of Food and Drugs Withdrawing Approval of the New Drug Applications for Lutrexin and Trexinest (36 FR 11763)

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE, FOOD AND DRUG ADMINISTRATION

(Docket FDC–D–123)

NDA Nos. 8–986 and 10–144

In the Matter of: LUTREXIN AND TREXINEST HYNSON, WESTCOTT & DUNNING, INCORPORATED.

Hynson, Westcott & Dunning, Incorporated ("HW&D") respectfully requests the Commissioner of Food and Drugs for a stay of his order withdrawing approval of the New Drug Applications (NDAs) for Lutrexin and Trexinest, pending timely filing by HW&D in the United States Circuit Court of Appeals of a petition that the order of the Commissioner be set aside, and pending the disposition of the petition by the Court. If this request for a stay is refused by the Commissioner HW&D will thereupon file with the Court of Appeals an application for such a stay and hereby requests the Commissioner to stay his withdrawal order pending the decision of the Court of Appeals upon such application.

The order of the Commissioner withdrawing approval of the NDAs is dated May 31, 1971, effective upon that date. The order was published eighteen days later in the Federal Register of Friday, June 18, 1971, when it first became available to HW&D and its counsel.

1. *Safety.* Lutrexin and Trexinest were accepted by FDA as safe when the agency permitted the NDAs for the drugs to become effective on December 23, 1953, and March 23, 1956,

respectively. Experience has confirmed the safety of the drugs since the NDAs became effective.

The affidavits of Doctors Bickers, Gratton, Majewski, Rezek, and Trythall, which are before the Commissioner, all testify to the safety (and effectiveness) of Lutrexin. These affdavits are only examples of the many expressions of OB/Gyn physicians who have made known to HW&D their conviction of the safety (and effectiveness) of the drug.

Dr. Willard M. Allen, a member of the NAS/NRC Panel, which evaluated Lutrexin stated, in a letter which is attached to Dr. Dunning's letter to Commissioner Edwards dated January 22, 1970—

> The clinical evidence which you have submitted and which I have read carefully, does indicate that Lutrexin is beneficial in the three conditions for which it is recommended.
>
> * * * * *
>
> Lutrexin, since it contains an active principle which relaxes the uterus should be available for the treatment of premature labor and should continue to be available until such time as a fully rational and effective treatment has been discovered.
>
> I can say with complete candor, that the effectiveness as judged by clinical trials of Lutrexin in the treatment of dysmenorrhea, threatened abortion and premature labor is as well established as other agents, i.e., delalutin, progesterone, stilbestrol or multivitamins.
>
> * * * * *
>
> I personally believe that the FDA should not exclude Lutrexin even though it may have the power to do so.

The affidavits before the Commissioner and the letter of Dr. Allen show not only that Lutrexin is safe but that there is a need for the drug in OB/Gyn practice.

2. HW&D proposes to seek judicial review of the Commissioner's order because it believes that Lutrexin is safe and effective and should be made available to the many OB/Gyn

physicians who regard it as useful or necessary in their practice. HW&D is entitled by statute to such review. In view of the undoubted safety of the drug, those physicians who desire to use it should not be precluded from such use until the issues here involved have been finally determined. Once the drug is removed from the market it is highly unlikely that it will be practicable to resume its distribution, with the result that it will be unavailable to the many physicians who have, since 1953, found it useful for their patients. Substantial legal and factual questions are involved in this matter. It is submitted that the prohibition of the marketing and use of the drug by physicians who want to use it before these questions are finally resolved would not be reasonable or in the public interest, and the denial of a stay would, under the circumstances, have the effect of a final decision insofar as the future use of the drug is concerned.

3. The stay herein requested is authorized by the Administrative Procedure Act (5 USC 705) pending judicial review when "justice so requires" and is within the contemplation of Rule 18 of the Federal Rules of Appellate Procedure. We believe that, under the circumstances of this case justice requires the stay herein requested.

Respectfully submitted,

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423 Washington Building,
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Counsel for
HYNSON, WESTCOTT & DUNNING,
Incorporated.

July 1, 1971.

36 F.R. 17371 (August 28, 1971)

FOOD AND DRUG ADMINISTRATION

[Docket No. FDC–D–123; NDA No. 8–986, 10–144]

HYNSON, WESTCOTT & DUNNING, INC.

LUTREXIN TABLETS, TREXINEST TABLETS; NOTICE OF DENIAL OF PETITION TO STAY EFFECTIVE DATE OF ORDER WITHDRAWING APPROVAL OF NEW-DRUG APPLICATIONS

The petition of Hynson, Westcott & Dunning, Inc. (HW & D) for a stay of the order withdrawing approval of new-drug applications Nos. 8–986 and 10–144 for its drugs containing lututrin is, after consideration of all the data offered by HW & D to support continued marketing of these preparations, denied for the following reasons:

1. Since 1966 HW & D has had repeated opportunities to come forward and present evidence derived from adequate and well-controlled clinical investigations demonstrating that lututrin is effective for its intended uses and has repeatedly failed to provide such data. No acceptable scientific data to support the efficacy claims made for these preparations was presented to either the National Academy of Sciences-National Research Council or the Food and Drug Administration.

2. There is no acceptable scientific data showing that lututrin has any biological activity in humans. To the contrary, there is evidence that lututrin is destroyed by hydrolysis due to the action of the gastric enzymes before it can pass the membrane barrier of the intestinal mucosa and be absorbed into the blood stream.

3. While lututrin is not a highly toxic pharmacologic agent—actually it appears to be inert—its use in patients exposes them to drug therapy without any concomitant possibility of therapeutic benefit.

4. In respect to the drug Trexinest, HW & D did not attempt to offer evidence that either component of that fixed ratio combination drug contributes to the claimed efficacy of the drug.

Dated: August 18, 1971.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc. 71-12645 Filed 8-27-71; 8:52 a.m.]

Petition to Set Aside Order of Commissioner of Food and Drugs

Hynson, Westcott & Dunning, Incorporated, hereby petitions the Court to set aside the Order of the Commissioner of Food and Drugs withdrawing approvals of new drug applications for Petitioner's drugs Lutrexin Tablets and Trexinest Tablets. The Order, which is dated May 31, 1971, recites that it is effective on the date of signature. It was filed with the Office of the Federal Register on June 17, 1971, and was published in the Federal Register of June 18, 1971 (36 FR 11763).

Respectfully submitted,

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Certified List of Record Pursuant to Rule 17(b) of the Federal Rules of Appellate Procedure

I hereby certify that following material comprised the record upon which the Order, dated May 31, 1971, was based and upon which judicial review is sought in this proceeding:

1. New Drug Application No. 10–144 (Trexinest) consisting of one file volume totaling approximately 300 pages.
2. New Drug Application No. 8–986 (Lutrexin) consisting of three file volumes totaling appproximately 400 pages.

3. Drug Efficacy Study Implementation Announcement regarding Lututrin published in the Federal Register on May 24, 1968 (33 F.R. 7701); 1 page.

4. Letter (with enclosure) dated July 12, 1968, from Bruce J. Brennan and John K. Worley to Herbert L. Ley, Commissioner of Food and Drugs; 4 pages.

5. Letter dated July 23, 1968 from Herbert L. Ley, Commissioner of Food and Drugs, to Bruce J. Brennan and John K. Worley; 1 page.

6. Letter dated July 26, 1968 from Bruce J. Brennan and John K. Worley to Herbert L. Ley, Commissioner of Food and Drugs; 2 pages.

7. Letter dated August 12, 1968 from Herbert L. Ley, Commissioner of Food and Drugs, to Bruce J. Brennan; 2 pages.

8. Notice of Opportunity for Hearing, Hynson, Westcott and Dunning, Inc. Lutrexin Tablets, Trexinest Tablets published in the Federal Register on March 22, 1969 [34 F.R. 5556]; 1 page.

9. Letter dated April 18, 1969 from Hynson, Westcott and Dunning, Inc. to Beryl McCullar, Hearing Clerk; 1 page.

10. Letter consisting of 8 pages dated October 16, 1970 from Edward Brown Williams to Beryl McCullar, Hearing Clerk and enclosing the following:

A. Hynson, Westcott and Dunning's Complaint for Declaratory Judgment and Injunctive Relief consisting of 25 pages filed August 19, 1969 in the United States District Court for the District of Maryland (Hynson, Westcott and Dunning, Inc. v. Finch, C.A. No. 21112) including three exhibits: (1) Drug Efficacy Study Implementation [33 F.R. 7701]; 1 page; (2) Notice of Opportunity for Hearing [34 F.R. 5556]; 1 page; (3) Letter of Hynson, Westcott and Dunning dated April 18, 1969, 1 page.

B. Hynson, Westcott and Dunning's Memorandum in Opposition to Defendants' Motions to Dismiss and in the Alternative for Summary Judgment (C.A. No. 21112) consisting of 56 pages, with the following exhibits: (1) Exhibit I. Affidavit of William M. Bickers, M.D., with curriculum vitae (Exhibit A) and list

of publications; 10 pages. (2) Exhibit II. Affidavit of Richard R. Gratton, M.D., with curriculum vitae (Exhibit A) and a copy of paper by Dr. Gratton entitled, "Treatment of Infertility and Prematurity Pregnancy Problems"; 13 pages. (3) Exhibit III. Affidavit of Fred B. Gray, M.D., with clinical report entitled, "Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases"; 11 pages. (4) Exhibit IV. Affidavit of Joseph T. Majewski, M.D., with curriculum vitae and list of publications (Exhibit A), and copies (Exhibits B, C, and D) of papers by Dr. Majewski, entitled, "A Uterine Relaxing Factor for Premature Labor", "Further Experiences with a Uterine Relaxing Hormone in Premature Labor", and "Statistical Evaluation in the Reduction of the Incidence of Prematurity"; 21 pages. (5) Exhibit V. Affidavit of George H. Rezek, M.D., with curriculum vitae and list of publications (Exhibit A), and copies of two papers (Exhibits B and C) by Dr. Rezek entitled, "The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea" and "Lutrexin in the Treatment of Premature Labor"; 16 pages. (6) Exhibit VI. Affidavit of Joseph F. Sadusk, M.D., with curriculum vitae (Exhibit A), list of publications (Exhibit B), and copy of paper (Exhibit C) by Dr. Sadusk entitled, "The Definition of the Efficacy of a Drug Under the Law"; 23 pages. (7) Exhibit VII. Copy of letter dated January 22, 1970, from Hynson, Westcott and Dunning to Commissioner Edwards, with attached copy of letter dated December 10, 1969, from Willard M. Allen, M.D., to J. H. F. Dunning, President of Hynson, Westcott and Dunning (Exhibit A); 12 pages. (8) Exhibit VIII. Commissioner Edwards' reply undated to Dr. Dunning's letter of January 22, 1970; 1 page.

C. Copy of Motion of Plaintiff for Continuance; 4 pages.

D. Affidavit of Sylvester W. Trythall, M.D., dated September 14, 1970, with curriculum vitae and list of publications; 8 pages.

E. Letter dated May 19, 1970, from Commissioner Edwards to Hynson, Westcott and Dunning; 1 page.

F. Letter dated June 10, 1970, from J. H. F. Dunning to Commissioner Edwards; 2 pages.

G. Transcript of Hearing on Defendants' Motions to Dismiss and in the Alternative for Summary Judgment in C.A. No. 21112 (D. Md.); 37 pages.

H. Certified copy of Order of Dismissal entered on September 11, 1970, in C.A. No. 21112 (D. Md.); 2 pages.

11. Order Withdrawing Approval of New Drug Applications 8–986 and 10–144 published in the Federal Register on June 18, 1971 [36 F.R. 11763]; 3 pages.

12. Letter and Petition for a Stay of the Order Withdrawing New Drug Applications 8–986 and 10–144 from Counsel for Hynson, Westcott and Dunning to Beryl McCullar, Hearing Clerk, dated July 1, 1971; 4 pages.

13. Notice of Denial of Petition to Stay Effective Date of Order Withdrawing Approval of New Drug Applications 8–986 and 10–144 published in the Federal Register on August 28, 1971 [36 F.R. 17371]; 1 page.

I further certify that the above named and described materials are being held by me on behalf of the Clerk of this Court, in the Office of the Hearing Clerk, subject to further order of the Clerk of this Court.

[SEAL] (S) Charles C. Edwards,
CHARLES C. EDWARDS, M.D.,
Commissioner of Foods and Drugs.

ABSTRACT

In the treatment of infertility and prematurity problems, uterine irritability and contractility are part of a complex syndrome which must be recognized early if viability of the fetus is to be obtained.

The results obtained over approximately a ten-year-period in 219 patients with a history of from 1 to 10 (for the most part 1 to 5 previous pregnancy complications) are presented.

The improved birth rate following institution of aggressive therapy is shown.

The Treatment of Infertility and Prematurity Pregnancy Problems

RICHARD R. GRATTON, M.D.

In the practice of infertility, gestation, once established in the previously infertile female, must be maintained and the fetus brought to viability.

The evaluation of any treatment or treatments requires a comparison with the spontaneous fertility rate. This fact has been a major stumbling block in the assessment of regimens used to treat infertility.

Since the etiological factors which may cause the premature emptying of the uterus are many, it is logical to assume that no one type of treatment can be expected to take care of all causative factors. Careful analysis of all probable causal factors results in more specific and intensive treatment of them.

Uterine irritability and contractility are part of a complex syndrome which must be recognized early if a threatened premature delivery is to be avoided.

Our practice deals for the most part with difficult problem cases and every pregnancy is considered as a possible cause of habitual abortion or premature labor. Prior to the institution of the use of Lutrexin as the major drug in treating these problem cases, less than 50% viable babies resulted. With the use of Lutrexin, a significant improvement occurred—about 80% viable babies were obtained.

Materials and Methods

Prior to the introduction of Lutrexin therapy, patients were treated as follows: Multivitamins, Vitamin C 250 mgs. daily, Thyroid, Progesterones—orally, bucally or vaginally twice weekly, Stilbestrol 25 mg. (E.C.) 1–4 tablets per day.

Patients were treated with Lutrexin as follows: In early pregnancy, if the uterus was irritable or retroverted and knee-chest exercises and/or a pessary was used, the Lutrexin dosage was 1 tablet twice a day, or 1 tablet four times a day.

At 5–6 months of pregnancy, if uterine contractions occurred, the amount of Lutrexin was increased to as much as 8 tablets per day.

In premature labor, the dosage schedule of Lutrexin was 12 tablets every hour for 8–24 hours. If contractions ceased, Lutrexin was maintained at 8–24 tablets each day until term.

Other treatment given included: (1) Provera 10 mg. ½ or 1 tablet once or twice daily; (2) Vitamin C 250–500 mg. daily; (3) Multivitamins daily; (4) Thyroid grains 1–2 daily in the first three months of pregnancy; (5) Progesterone in oil 50 mg. I.M. every 1–2 weeks until the fifth month of pregnancy.

Results

Although there were 286 patients treated as described under Materials and Methods, 67 of these had not been pregnant before and were excluded from Table I, which presents the patients on the basis of the number of previous pregnancies and live births prior to the inception of Lutrexin therapy as well as the live births resulting when patients were treated with Lutrexin.

In Table II, the data of the previous Table I have been combined to facilitate statistical evaluations. It can be seen that in the 219 patients with a total of 446 pregnancies, there were only 46% live births prior to the use of Lutrexin. Following the administration of Lutrexin, the percentage of live births in these same patients was 79.8% with a probability of .001.[1] Probabilities ranging from .001 to .05 were observed in women with one to five previous pregnancies who had been treated with Lutrexin. No statistical tests for significance were made with six or more pregnancies because of the small sample.

Discussion

After using Lutrexin in a small number of problem cases and noting the apparent beneficial effect, it was decided to utilize this drug in all cases of premature labor, threatened abortion and habitual abortion. Experience gained over approximately ten years has amply shown the value of Lutrexin in the treatment of such patients. Before using this drug, only 46% live births were obtained in 446 pregnancies, whereas with the use of Lutrexin, 79.8% live births were achieved. The differences noted with, and without, Lutrexin were highly significant ($P=.001$) in the entire study herein reported. Signifi-

cant differences (P=.001 to .05) were observed in patients with one to five previous pregnancies.

In this study, the patients have served as their own controls. This practice has been criticized by Goldzieher.[2] On the other hand, the use of double-blind studies, although very satisfying from a purely scientific point-of-view may, as indicated by Allen [3] "violate morality as well as common sense". Having experienced relatively poor results in the case of these difficult problem cases in the past, the beneficial effects resulting from the administration of Lutrexin to the first number of cases on which it was tried, it seemed desirable to extend it to others. The denial of such treatment to others to obtain more scientifically acceptable data was unacceptable in view of the safety of the drug as well as reports of its effectiveness.

Another argument that might be made as to the validity of the data is that there have been some unknown factors that have suddenly caused the patients to show a higher percentage of live births than observed before, unrelated to Lutrexin therapy. If such factors were operative, it might be anticipated that there would be some lowering in the prematurity rate as part of an overall improvement in the pregnancy state. However, no evidence for this was found. The prematurity rate in the United States has been about 6–7% for many years.[4] This is quite similar to the rate prevailing in the San Francisco area from which the patients in this study were drawn.

No other factors could be found that might explain the significant increase in percentage of live births other than the use of Lutrexin.

It is felt that the good results obtained in this study are related to the institution of Lutrexin therapy as early as possible, particularly when there is a history of repeated early abortions or premature labors when there is no cervical incompetence or when retroversion of the pregnant uterus is found.

Summary

1. The results obtained in the treatment of 219 women with a past history of prematurity, threatened and habitual abortion with Lutrexin are presented.

2. A live birth rate of 80% was obtained with the use of Lutrexin as compared to 46% prior to the use of this drug.

495-151—73——7

References

1. Maitland, D.: Canada Journal of Research, 26:1–166, February 1948.
2. Goldzieher, J. W.: J.A.M.A., 188:131–134, May 18, 1964.
3. Allen, W. M.: Rocky Mt. Medical Journal, 62: 31–35, August 1965.
4. Majewski, J. T. and Pennings, T. L.: Obstetrics & Gynecology, 5:649–652, May 1955.

Table I.—*Presentation of study group with respect to previous pregnancies live births and results following Lutrexin treatment*

Prior to Treatment with Lutrexin					Following Treatment With Lutrexin	
No. of Cases	No. Previous Pregnancies	No. Live Births	Total Pregnancies	Total Live Births	Live Births	Deaths
41	1	0	41	0	27	14
65	1	1	65	65	54	11
16	2	0	32	0	13	3
21	2	1	42	21	18	3
20	2	2	40	40	17	3
9	3	0	27	0	6	3
8	3	1	24	8	8	0
5	3	2	15	10	5	0
5	3	3	15	15	4	1
3	4	0	12	0	1	2
5	4	1	20	5	5	0
3	4	2	12	6	3	0
3	4	3	12	9	3	0
1	5	0	5	0	1	0
4	5	1	20	4	2	2
3	5	2	15	6	3	0
1	5	3	5	3	1	0
2	6	2	12	4	2	0
1	6	3	6	3	0	1
1	7	0	7	0	0	1
1	9	3	9	3	1	0
1	10	3	10	3	1	0
219	--	-	446	205	175	44

TABLE II.—EVALUATION OF EFFECTIVENESS OF LUTREXIN THERAPY

Prior to Treatment with Lutrexin					After Treatment with Lutrexin			
No. of Cases	No. Previous Pregnancies	Total Pregnancies	Total Live Births	% Live Births	Total Live Births	% Live Births	Chi Square	Probability
106	1	106	65	61.3	81	76.4	5.2	.05
57	2	114	61	53.5	48	84.2	14.2	.001
27	3	81	33	40.7	23	75.2	14.3	.001
14	4	56	20	35.7	12	85.7	11.8	.001
9	5	45	13	28.9	7	77.8	5.7	.02
3	6	18	7	38.9	2	66.7	----------	----------
1	7	7	0	0.0	0	0.0	----------	----------
1	9	9	3	33.3	1	100.0	----------	----------
1	10	10	3	30.0	1	100.0	----------	----------
219	----------	446	205	46.0	175	79.8	----------	.001

The undersigned hereby certifies that the foregoing is a true and correct copy of his paper entitled *The Treatment of Infertility and Prematurity Pregnancy Problems* (1968, unpublished).

Date: March 11, 1970.

/s/ Richard R. Gratton, M.D.
RICHARD R. GRATTON, M.D.

A Uterine Relaxing Factor for Premature Labor

[*Reprinted from Vol. 5, No. 5, May 1955*]

OBSTETRICS AND GYNECOLOGY

J. T. Majewski, M.D., and T. Jennings, M.D.

Premature delivery occurs in 6 to 7 percent of total births. Prophylaxis against premature labor seems desirable to prevent the difficult task of caring for a premature infant.

In recent years, interest has increased in the effects of hormonal changes on the initiation of labor. In this study, a uterine relaxing factor (LUTREXIN) was administered clinically to 21 patients judged to be in premature labor and succeeded in giving a favorable result in 80% of the cases. Our results show one method of treatment that may lead to the salvage of a number of infants.

Krantz, Bryant, and Carr in 1950 demonstrated the ability of a substance found in aqueous extracts of sow corpora lutea to diminish the tone and abolish contractions of the guinea pig uterus in situ. This material has been studied chemically by Felton, Frieden, and Bryant (1953) and its effect in the treatment of dysmenorrhea has been investigated by Rezek and by Jones and Smith. The present study relates to our work in utilizing this material in attempts to reduce the high fetal death rate associated with premature labor.

It is generally agreed that between 6 and 7 per cent of total births have, consistently, been premature. In the hospital in which this study was conducted, the prematurity average is 9.7 per cent by maternal history and 6.2 per cent by weight. The criterion of prematurity is a birth weight less than 2300

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Gm. The fetal death rate also closely parallels that of other institutions, being 99 per cent for infants of 750 Gm. and 7 per cent at 2000 Gm. or over. The total death rate is calculated as 30 per cent.

The solution to this problem of a high premature fetal mortality has been elusive. The ideal method seems to be, as Potter states, that of prophylaxis against premature labor, thus circumventing the very difficult task of caring for a premature infant.

Many theoretical explanations have been given of the mechanics of the onset of labor, but as yet all have remained hypothetical. These theories encompass almost every aspect of parturition. A few attribute to the uterus, with its increasing size and growing irritability, the responsibility for producing spontaneous labor. Other theories are concerned with the environment of the cervix and lower segment of the uterus near term, the carbon dioxide content of the blood, and senility of the placenta.

In recent years, interest has increased in the effects of hormonal changes on the initiation of labor. There have been several revealing studies on this subject, including an important observation by Snyder. He prolonged the duration of pregnancy in the rabbit by inducing ovulation near term and concluded that the retention of the fetus in the uterus is under hormonal control and that parturition coincides with the termination of the life-cycle of the corpus luteum. In a parallel study, Heckel and Allen found that 1.5 mg. progesterone injected subcutaneousy in rabbits not only may delay but even prevent parturition. Despite the evidence presented by these authors it is our belief that the trigger mechanism of labor is multiple, being hormonal, fetal, placental, and local in uterine and cervical changes.

MATERIAL

In this preliminary study, the uterine relaxing factor was administered to 21 patients. All but 2 of the patients were treated in the hospital. The 2 exceptions were given medication and treated at home with no restriction of activity. Only individuals clinically adjudged to be in labor were selected, the choice being made by the attending physician and the

resident. Patients who were well advanced in labor (beyond 3 cm. dilatation) were not given the uterine relaxing factor. Those who terminated their pregnancy prematurely because of abruptio placentae, or central placenta previa likewise were excluded from this study. Other than these restrictions, there were no attempts to exclude patients for such reasons as ruptured membranes or monstrosities.

RESULTS

The hopsital wherein the study was conducted has, as stated, a premature birth rate of 9.7 per cent by length of gestation and 6.2 per cent by weight. During a four-month period in 1953, the premature birth rate by history was 9.7 per cent in 1601 deliveries. During the same period, there were 101 premature births by weight, or 6.3 per cent. During this study there were, in a comparable period during 1954, 154 births premature by history in a total of 1631 deliveries, for a percentage of 9.4. In our series of patients using the uterine relaxing factor the number of premature deliveries by weight was reduced during these four months to 80 (4.9 per cent)—a saving of 21 premature deliveries. These included both vaginal and abdominal deliveries.

TABLE 1.—*Summary of experimental series*

Case	Pains on entrance			Cervix		Presenting part	Station	Membrane	Bloody show
	Type	Freq.	Duration (hr.)	Dilat.	Efface.				
1	Mod	2 min	1	1 Fb	Soft	Vertex	−3	Intact	0
2	Mod	2 min	4	1 Fb	Thick	Vertex	−1	Intact	0
3	Mod	3 min	4	Not reached		Vertex	−3	Intact	±
4	Mod	10 min	9	2 Fb	Soft	Vertex	0	Intact	0
5	Mild	Irreg	3	1 Fb	Thick	Vertex	−3	Intact	0
6	Mild	Irreg	2	Closed	Thick	Vertex	−3	Intact	±
7	Mild	Irreg	2	Closed	Thick	Vertex	−3	Intact	±
8	Mild	2–3 min	3	1 Fb	Thick	Vertex	−1	Intact	0
9	Mild	Irreg	Indef.	1 Fb	Thick	Vertex	−3	Intact	±
10	Mild	4–6 min	6	Closed	Thick	Vertex	−1	Intact	0
11	Mild	15 min	?	1 Fb	Thin	Vertex (twins)	0	Bulging	±
12	Mild	Irreg	3	2 Fb	Thick	Vertex	−1	Intact	±
13	Mild	5 min	2	2 Fb	Thin	Vertex	−3	Intact	±
14	Severe	3 min	5	1½ Fb	Soft	Vertex	0	Ruptured	±
15	Mod	5 min	4	No		Rectal		Intact	±
16	Mod	5 min	3	1½ Fb	Soft	Vertex	−1	Intact	±
17	Mild	5 min	6	1½ Fb	Soft	Vertex	0	Intact	0
18	Mod	4 min	4	2 Fb	Soft	Vertex	0	Ruptured	0
19	Mild	Irreg	Indef.	1 Fb	Soft	Vertex	−2	Intact	0
20	Mild	Irreg	Indef.	1 Fb	Soft	Vertex	−3	Intact	0

NOTE: Table 1 continues on page 96.

TABLE 1.—*Summary of experimental series*—Continued

Case	Grav.-Para.	E.D.C.	Gestation (wk.)	Other sedation	Outcome	Date of delivery	Wt. of baby (Gm.)	Wt. of previous baby (Gm.)
1	3-2	6- 8-54	35	None	Pains lasted 3 da	39 wks	2792	2807–3090.
2	5-4	3- 1-54	35	None	Pains lasted 24 hr	41 wks	3459	2353–2722.
3	5-3	3- 5-54	38	None	Pains lasted 8 wk	41 wks	3459	2495–3118.
4	1-0	5- 4-54	30	None	Pains lasted 20 hr	33 wks	2325	None.
5	5-3	3-28-54	34	None	Pains lasted 15 hr	39 wks	3685	3062–3629.
6	2-1	4- 7-54	27	None	Pains lasted 12 hr	39 wks	3289	2863.
7	3-2	2-15-54	25	None	Pains lasted 24 hr	42 wks	3430	Unknown.
8	3-2	1-20-54	28	100 mg	Pains lasted 7 hr	38 wks	2920	2211–2948.
9	2-1	1- 1-54	32	None	Pains lasted 8 hr	39 wks	3260	3402.
10	3-2	12-31-53	32	None	Pains lasted 6 hr	39 wks	2920	3289.
11	2-1	1-23-54	26	None	Pains lasted 3 hr	28 wks	624, 652	2920.
12	2-1	2-21-54	34	None	Pains lasted 3 hr	38 wks	2892	3260.
13	3-2	4- 1-54	34	None	Pains lasted 3 hr	37 wks	2070	2240–2948.
14	2-0	3- 8-54	24	None	Delivery 4 hr	24 wks	907	
15	5-4	4-28-54	34	None	Delivery 3 hr	34 wks	1531	2580–3402.
16	2-0	3-29-54	22	None	Delivery 5 da	22 wks	680 Stillborn	
17	1-0	2-27-54	32	None	Pains lasted 5 hr	38 wks	2325	
18	1-0	3- 6-54	36	None	Delivery 10 hr	36 wks	2041	
19	3-2	4-28-54	30	None	Pains lasted 5 hr	39 wks	3062	1928–2381.
20	6-1	6- 1-54	23	None	Pains lasted 2 hr	29 wks	1417	3345.

The plan of dosage was derived by clinical trial and error. Upon admission the patient was prepared for normal vaginal delivery. The perineum was shaved and cleaned, and the patient was placed in bed. Enema was excluded. No attempts were made to inform the patients of the therapy or of the desired end results. No attempts were made to give the patients sedation, although some received small doses of barbiturates. The pains were recorded, in most instances, by competent observers who evaluated the contractions clinically rather than by relying upon the patient's statement.

The dosage of the uterine relaxing factor, after a few trials, was fixed at 4000 units initially, followed in one hour by 3000 units, and by 1000 units hourly thereafter until contractions ceased both clinically and symptomatically. All doses were given orally. No side effects were observed.

The results are tabulated in Table 1. There were 4 deliveries in spite of the therapy, giving a favorable result in 80 per cent of the cases. Some patients were of sufficient interest to deserve separate mention.

Case 11 was a multipara with a multiple pregnancy, the first baby being in vertex presentation at zero station. Lutrexin* was started upon entry to the hospital, at which time she was 1 fingerbreadth dilated with membranes bulging. The pains continued for approximately 3 hours and gradually subsided. At the time when contractions ceased, the cervical os was 3 cm. dilated with membranes still bulging. The patient was kept under therapy and allowed to ambulate. She was discharged after one week, only to return in another and deliver twins of 624 gm. and 652 gm. weight. As long as the patient was under the uterine relaxing factor the uterus was quiescent. However, when therapy was discontinued, uterine irritability and eventual labor returned.

Case 19 was a gravida III who had been previously delivered of a 2381 gm. baby by cesarean section because of cephalopelvic disproportion. Her second delivery, performed vaginally, was of an infant weighing 1928 gm. at 34 weeks' gestation. During the third pregnancy she noted frequent contractions and irritability of the uterus at 30 weeks. This was the same pattern that had occurred with the two previous pregnancies.

*Hynson, Westcott & Dunning, Inc., Baltimore, Maryland.

She was placed on Lutrexin therapy at home with no restriction of activity, and her pregnancy was terminated by an elective cesarean section at 39 weeks, the infant weighing 3062 gm. at birth. In this patient, it is interesting to note, if therapy was not given the contractions would become noticeable.

It is, of course, true that Hicks' sign and the softening tendency of the cervix in the last trimester may confuse the picture. Some of our patients may have been experiencing "false labor" pains. There have been in the past and there undoubtedly will be in the future many women saved from premature delivery by watchful expectancy and bed rest. But even after all these allowances have been made, we still feel that our figures have real significance. If the premature birth rate can be reduced the number of salvaged babies soon will be of the utmost importance.

The purpose of this paper is not to propose the uterine relaxing factor as a panacea for all evils connected with premature labors. There are too many factors, including the emotional, concerned in the precipitation of early labor for one remedy to be sufficient. However, our results show one method of treatment that may lead to the salvage of a number of infants.

References

1. Felton, L. C., Frieden, E. H., and Bryant, H. H. The effects of ovarian extracts upon activity of the guinea pig uterus in situ. *J. Pharmacol. & Exper. Therap. 107*:160, 1953.
2. Heckel, G. P., and Alien, W. M. Prolongation of pregnancy in the rabbit by the injection of progesterone. *Am. J. Obst. & Gynec. 35*:131, 1938.
3. Jones, Georgeanna S., and Smith, F. Treatment of the dysmenorrhea symptom complex: A preliminary report on the efficacy of a uterine "relaxing factor." *Am. J. Obst. & Gynec. 67*:628, 1954.
4. Krantz, J. C., Jr., Bryant, H. H., and Carr, C. J. The action of aqueous corpus luteum extract upon uterine activity. *Surg. Gynec. & Obst. 90*:372, 1950.
5. Potter, E. Pathology of the Fetus and Newborn. Chicago, Ill., Yr. Bk. Pub., 1952.
6. Rezek, G. H. The effect of a new potent uterine relaxing factor of the corpus luteum in the treatment of dysmenorrhea. *Am. J. Obst. & Gynec. 66*:396, 1953.
7. Snyder, F. F. Prolongation of pregnancy and complications of parturition in the rabbit following induction of ovulation near term. *Bull. Johns Hopkins Hosp. 54*:78, 1934.

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The undersigned hereby certifies that the foregoing is a true and correct copy of a paper authored by him and T. Jennings, M. D. entitled *A Uterine Relaxing Factor for Premature Labor*, which was published in Obstetrics and Gynecology, Volume 5, No. 5, May, 1955.

J. T. MAJEWSKI, M. D.

Date: .....

Further Experiences With a Uterine-Relaxing Hormone in Premature Labor

J. T. Majewski, M.D., and T. Jennings, M.D.

An enlarged study was made of the effectiveness of the uterine relaxing hormone LUTREXIN® in premature labor. Contractions were halted in 54 of 79 patients, or 68.4%.

Obstetricians have long sought a means of controlling prematurity, which is believed to cause half of the 150,000 neonatal deaths recorded in the United States each year. Because the etiologies of labor remain unknown, despite the many theoretical explanations advanced, the control of prematurity, once labor has begun, has been unsuccessful.

In an earlier publication we discussed the use of the uterine-relaxing hormone found in the aqueous extracts of the sow corpora lutea in an attempt to halt premature labor in a series of 20 patients.[1] We were able to report success in 16 patients (80 percent). It was decided to continue the project and we are now prepared to report the use of the uterine-relaxing hormone in an additional 68 patients. While results in the total group of 88 patients are somewhat less favorable than in the smaller group alone, they are encouraging.

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[1] From the Department of Obstetrics and Gynecology, Marquette University School of Medicine, Milwaukee, Wis.

Lutrexin for this study furnished by Hynson, Westcott & Dunning, Inc., Baltimore, Md.

MATERIAL

Eighty-eight patients, both primiparas and multiparas, who were clinically judged to be in labor before the thirty-eighth week of pregnancy, received the uterine-relaxing factor. Evaluation of the patient in labor proved to be the most difficult part of the study. A progression of cervical dilatation, effacement of the cervix, or a progressive descent of the presenting part were deemed indications of "true" labor. In an attempt to exclude patients in false labor, those experiencing grossly irregular uterine contractions, simple backache, an isolated bloody show, or general bearing-down sensations of the pelvis were not given the medication. Patients who entered the hospital with a cervical dilatation of 3 cm. or more were judged to be well advanced in labor and were excluded from the study. The patient's emotional condition was not taken into consideration in the selection of subjects. Those individuals whose labors were complicated by an abruptio placentae or a placenta previa are not included in our statistics, since continuing a pregnancy under these conditions is of doubtful value and at times hazardous.

Not all patients who entered the hospital in premature labor were subjects of this study since this hospital is an institution of private care and the final choice rested with the attending physician.

Two of the patients included in the study were not under hospital supervision, but were treated at home; they were ambulatory and were not restricted in activity.

METHOD

When a patient entered the hospital in premature labor she underwent the usual preparations for vaginal delivery except that no enema was given. No effort was made to inform her of the desired result of the therapy.

The uterine-relaxing hormone Lutrexin* was administered orally according to the plan worked out in our preliminary study. An initial dose of 4000 units was followed in 1 hour by 3000 units of 1000 units each hour thereafter until uterine contractions were eliminated.

*Hynson, Westcott & Dunning brand of lututrin.

TABLE 1.—*Response to Therapy*

[Percentages Based on Size of Groups at Various Weeks of Gestation]

Weeks of gestation	No. patients treated	Labors halted		Labors not halted	
		No.	%	No.	%
Up to 30	28	18	64.3	10	35.7
30–32	17	11	64.7	6	35.3
32–34	15	12	80	3	20
34–36	14	9	64.3	5	35.7
36–38	5	4	80	1	20

Whenever possible patients receiving the uterine-relaxing hormone were divorced from all other medications In some patients it was necessary to continue uterine-relaxing-hormone therapy for as long as it was desirable to postpone contractions.

RESULTS

Uterine-relaxing-hormone therapy successfully halted uterine contractions in 54 of 88 patients studied. For statistical purposes we have eliminated 9 patients in whom the medication was ineffective. Six of these were under the influence of the uterine-relaxing hormone for less than 3 hours before delivery. This we believe is too short a time to be a true test of the medication's effectiveness. The others eliminated delivered an anomalous fetus or had a prolapse of the umbilical cord, conditions in which a merely prolonged pregnancy would have had no value.

Table 1 presents the response of the entire study using the corrected total of 79 patients. Here the percentages are figured on the size of the groups at the various periods of gestation, rather than on the total number of patients in the study. Therapy proved successful in about 64 per cent of the patients whose pregnancies threatened to terminate before the thirty-second week. Other percentages listed may not be truly indicative of response because of the small size of the groups involved.

It should be noted that 45 of the 79 patients (56 percent) entered the hospital before the thirty-second week. Since delivery at this time almost universally connotes fetal disaster,

it is gratifying to note that 29 (64 per cent) of these patients were prevented from delivering at this precarious period despite the fact that labor would not be halted in 16.

Eleven of the 25 babies delivered prematurely when the uterine-relaxing hormone failed to halt labor weighed between 454 and 908 Gm. (Table 2). This weight is normal for babies born during the early part of the last trimester, when the majority of premature labors in our series occurred. The criterion of prematurity is a birth weight of less than 2300 Gm.

The subject of Table 3 is the length of labor in the 25 patients whose uterine contractions were not controlled by the uterine-relaxing hormone. It will be noted that the medication did not appear to lengthen labor in these patients. The length of time during which the uterine-relaxing hormone was administered and the dosage did not seem to be primary factors in the success or failure of the medication in halting labor.

Table 4 compares the total number of premature survivals, stillbirths, and neonatal deaths during the 15-month period the study was in progress. Group I represents those treated with the uterine-relaxing hormone. The increase in survival rests with the fact that labor was delayed, allowing infants to more closely approach maturity.

TABLE 2.—*Weights of babies delivered when uterine-relaxing hormone failed to halt labor*

Weight (Gm.):	*Number*
Up to 454	3
545–908	11
908–1362	4
1362–1816	4
1816–2270	3
2270–2500	0

TABLE 3.—*Length of labor following institution of therapy in 25 unsuccessful attempts*

Labor time:	*Number of patients*
4 hours	7
4–8 hours	3
8–12 hours	6
12–24 hours	6
28 hours	1
36 hours	1
5 days	1

TABLE 4.—*Premature births during a 15-month period*

	Group I*		Group II	
	No.	%	No.	%
Premature survivals	69	78. 4	220	71. 2
Premature stillbirths	5	5. 7	23	7. 4
Premature deaths (neonatal)	14	15. 9	66	21. 4
Total premature births	88	100. 0	309	100. 0

* Patients treated with uterine-relaxing hormone.

During the study 397 patients delivered prematurely. In a comparable length of time prior to the study there were 404 premature births. In Table 5 we see a comparison by weight of both groups, with Group I representing the study period. We believe it is significant that, while the total deliveries remains about the same, there is a reduction of Group I in the 2 lowest weight brackets. Weight is of great importance, of course, since a premature infant's chances of survival usually parallel his approach to normal birth weight.

TABLE 5.—*Premature totals*

	500–999 Gm.	1000–1999 Gm.	2000–2500 Gm
Group I*	42(10. 5%)	108(27. 2%)	247(62. 3%)
Group II	49(12. 1%)	125(31. 0%)	230(56. 9%)

* 379 cases, of which 88 were treated with Lutrexin.

DISCUSSION AND CONCLUSIONS

The results of the study recently completed are somewhat less favorable than the results of our preliminary study. In the earlier study the uterine-relaxing hormone halted labor in 16 of 20 patients (80 per cent). In our latest study, which includes the 20 studied earlier, the uterine-relaxing hormone halted contractions in 54 of 79 patients (68.4 per cent).

We found that it was not always possible to postpone labor as long as was desirable. In some patients contractions would return in a period of 4 to 6 weeks and delivery would follow

despite therapy. However, by delaying delivery for several weeks we were able to give 54 babies a longer time to gain weight and to develop within the uterus, thus increasing their chances of survival and lessening the possibility of their suffering from the congenital diseases so often associated with prematurity.

The effectiveness of the uterine-relaxing hormone varies greatly with the individual patients. When it halts labor, it does so in an average of 4 to 6 hours. When it fails to halt labor, it leaves the contractions completely unaffected. In some cases we found it necessary to continue uterine-relaxing-hormone administration in order to keep the uterus quiescent. When therapy was discontinued uterine contractions returned in these patients.

It is noteworthy that when the uterine-relaxing hormone fails, it does not complicate delivery by prolonging labor. No irregular contractions were noted following the administration of the hormone. This would seem to indicate that some unknown factor, antagnostic to the medication or capable of neutralizing its effects, is produced in the bodies of some patients, or perhaps in all patients, at some stage of labor. Another explanation may be that the uterus itself reaches a point in labor when it becomes unresponsive to medication.

We found no side effects either in the patients who were hospitalized or in those who received treatment at home. Voluntary muscles were unaffected. Bowel habits in the ambulatory patients remained the same, which would indicate that the smooth musculature of the gastrointestinal tract was likewise unaffected.

The uterine-relaxing hormone was found to be helpful in relieving Braxton Hicks contractions, which may become somewhat distressing during the last trimester.

The use of the uterine-relaxing hormone is not suggested as a remedy in all instances of threatened premature delivery. It is a temporary measure which may postpone delivery to a more desirable time. We believe that only when the true etiologies of labor are discovered can true therapeutic agents be developed.

It appears that premature labors in otherwise normal women are frequently precipitated by temporary conditions, such as

exterogenic pressure on the uterus, emotional excitation, excessive carbon dioxide in the blood following strenuous activity, and perhaps even uncontrolled intestinal peristalsis. If such a condition were present for a sufficient time, it seems possible that cyclic contractions could develop and lead to true labor. It is in the control of uterine contractions under such circumstances that the uterine-relaxing hormone can be most useful.

SUMMARY

In an enlarged study on the uterine-relaxing hormone, contractions have been halted in 54 of 79 patients, a total of 68.4 per cent. In our earlier small series, labor had been halted in 16 or 20 patients. By delaying delivery for several weeks we were able to give 54 babies a longer time to gain weight and develop within the uterus. The effectiveness of the uterine-relaxing hormone varies greatly with the individual patient. When it halts labor it does so in an average of 4 to 6 hours. When it fails to halt labor, it leaves the contractions completely unaffected.

No side effects were noted in any of the patients who received this therapy. It can be concluded that Lutrexin is successful in controlling uterine contractions, thus reducing the fatality rate for premature infants.

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Reference

1. MAJEWSKI, J. T., and JENNINGS, T. A uterine-relaxing factor for premature labor. *Obst. & Gynec.* 5:649, 1955.

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Date March 5, 1970.

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Statistical Evaluation in the Reduction of the Incidence of Prematurity

(By J. T. Majewski, M.D.)

Prematurity takes a devastating toll among newborn infants. Neonatal mortality rates for the years 1957 through 1966 ranged from 19.1 to 17.2 per 1,000.[1] In studies encompassing as many as 10,000 deliveries, the causes of prematurity were obscure in 60 to 70% of these cases.[2, 3] Because of the implication of these obscurities in his practice, the pediatrician is developing an entire specialty for the care of premature infants. A large number are normal infants who would have had a much better chance for life had they been born at or closer to term. As our ability to care for the infant increases, greater emphasis must be given to increased gestational time for threatening prematurity without jeopardizing the health of mother or infant. By adding to the precious days of gestation, we thus can further assure that not only the life of the infant may be salvaged, but the infant when born, because of added length of uterine incubation, is not plagued with the added misfortunes of mental variations, such as cerebral palsy, physical discoordination or a lessening of the acute definition of the major senses. In this consideration, it may be also admitted that it is nebulous at least to judge, predict, or accurately evaluate any clinical regime, because all are subject to human interpretations. However, certain criteria were employed in this evaluation, and crude as they may be, they are the only measuring devices that are available.

Usually the placebo double-blind study affords the ideal comparison to establish the validity of experimental results. The double-blind study is now academically "sacred", and other types of evaluations too often are not recognized as investigative. In clinical evaluations, the clinician is frequently encompassed in decisions which violate the rules of clinical morality. For instance, in lobar pneumonia, no clinician could risk treating alternating cases with an antibiotic and a placebo. To the clinician concerned with premature labor, it is doubtful that a double-blind study is of choice, and, under such conditions, he could violate sound medical ethics. During his recent tenure as Director of the Bureau of Medicine of the Food and Drug Administration, Dr. J. F. Sadusk, Jr., recognizing this difficulty, stated in part, "The use of other disciplines, such as statistics,

may provide the extra support to make the study an acceptable and convincing one." (4) Properly used and interpreted, statistics are one of the most powerful tools in the scientific armamentarium of the practicing physician.

Prematurity is undeniably present in 5 to 7% of all births, and the fetal wastage is definitely increased if these deliveries occur nearer to the age of viability, which has been stated at the 26th to the 28th week. There have been two papers published by the author, the first in 1955 [5], and the last in 1957 [6]. A therapeusis other than symptomatic therapy of a regime of Lutrexin was initiated on those who entered labor prematurely. This regime was tried and successfully, I believe, in controlling the labors and, thus, decreasing the fetal catastrophies. Work at the inception of this undertaking was being completed by Dr. G. H. Rezek [7] of Chicago, Illinois, on the usage of Lutrexin on patients who presented themselves with dysmenorrhea. A logical conclusion was drawn that this medication could be employed to control uterine cramps early in pregnancy. If it could control the rhythmical cramp-like action of the uterus in a nonpregnant stage, it might do the same in early labors. No solicitation by the manufacturer was made. The study was done with the cooperation of the Obstetrical department of St. Joseph's Hospital and Marquette University, Milwaukee, Wisconsin, and all of the results of the two papers were conducted by various members of the obstetrical residents staff and other interested staff members, all duly qualified diplomates of the American Board of Obstetrics and Gynecology.

In essence this report draws the clinical conclusion that the uterine relaxing hormone, Lutrexin, was effective in stopping labor in 86.7% of 75 patients who had previously, without this drug, given a salvage rate of only 51.9%. Further, a brief description of thirteen (13) primiparas who were treated with Lutrexin is given. Eleven of these or 84.6% delivered viable babies. It should be noted that when the hormone halted labor the effectiveness was noted in four to six hours, and when it failed, the labor progressed normally with no side effects. In fact, no untoward effects have been noted by the mother or the infant.

Diagnosis of Labor

The diagnosis of labor was dictated by the influence the contractions had upon the cervix. Initially, the patients that were used in this study were hospitalized and the progress duly re-

corded and observed by highly trained residents and the obstetrical nurses of the department. The mere statement of contractions by the patient was no criterion. The contractions had to be observed for length and duration and recorded, and the ultimate cervical dilatation had to be noted before the patient would be stated to be in labor. If the patient had cramps, but no effacement, dilatation of the cervix or both, she was not adjudged to be in labor. Placebo or pills for a double-blind study were not used because of hundreds of articles, and the hospital's own statistics, which had remained constant through the years, were used as comparison. The patient could not volunteer information. It had to be observed or it was not accepted. In this study, only patients who reached the 26th week of pregnancy, with effacement of the cervix accompanied by dilatation, were included. No patient was thought to be beyond 38 weeks gestation, or 2 weeks prior to the estimated date of confinement.

The uterine relaxing hormone lututrin* was administered orally, 12,000 units stat, followed by 9,000 units hourly until contractions ceased, or until delivery or abortion occurred. The only ancillary medication given to any patient was a small dose of Demerol, which never exceeded 50 mg. No patient received more than two such injections.

Report of Clinical Results

Generalizations gleaned from the study show that there was an 86.7% salvage rate among women who were multiparas, and 84.6% among primiparas, for a general survey of 86.4% success in the 88 patients (see Tables I and II). Chi square was calculated for the group of multiparas, giving a result that was highly significant, $P<.001$.

There were three sets of twins in this study, and two were successful. The only unsuccessful attempt was to the fine wife of the author, who went into labor at 32 weeks and delivered in 10 hours, despite the attempt to thwart labor.

Five (5) of the multiparas were subjected to circlage suture; four of these carried to term. The one failure was a patient who was sutured approximately the 10th week of gestation; this pregnancy was terminated suddenly by an abruptio placenta. Furthermore, this patient has been pregnant 7 times. Although this individual delivered a normal infant on first pregnancy,

*Lutrexin, Hynson, Westcott & Dunning, Inc., Baltimore, Md.

subsequent pregnancies aborted or delivered spontaneously about the 20th to 26th week of gestation. Presently, this same individual is about 5 weeks from term after a Mersilene tape suture was employed when examination revealed bulging membrances and definite dilation of the cervix. Although the number of case histories in this category is small (5), the salvage of 80% of these pregnancies correlates well with the 81.5% reported by Jeremias and Trythall in a larger series.[8] On the other hand my results contrast with a 63% salvage rate recently reported with the use of a progestin and isoxsuprine hydrochloride, and this is a significant contrast to the 25% salvage rate obtained prior to treatment.[9]

Five (5) of the multiparas were classified as habitual aborters, having experienced three or more abortions prior to coming under my puryiew. In these cases, the patients were placed on medication as early as the 3rd month. Of these 5 patients, 4 carried to term.

In the 13 primiparas, 11 or 84.6% carried to term (Table II). It is interesting to note in case no. 3 that following the first successful pregnancy when Lutrexin was used, the next pregnancy was not successful when Lutrexin was not administered. The third pregnancy, with the use of Lutrexin, had a successful outcome.

Summary and Conclusion

In a 10-year study of private patients, the uterine relaxing hormone, lututrin, has proved effective in 84.6% of 88 treated patients. Included were diabetics, RH factor problems and patients who had abruptio placentas. From these findings, it can be concluded that lututrin is successful in controlling abnormal uterine contractions.

A few positive results should be worth noting from this study. The medication used is not a panacea for all the ills of labor. It can be extremely useful in certain circumstances and the removal of this medication, although it has only a clinical background, will reduce the chances of the fetus of a premature labor to the time prior to lututrin of 43% to 45%. Where there is placental pathology, such as previa or abruptio, lututrin is not effective in diminishing the labors. However, in scanning the results, it is curious fact that some habitual aborters were aided in delivering a youngster in a viable time area.

Other medications have been employed by me, such as stilbestrol, aqueous corpus luteal extracts, vasodilan and delalutin, and the results were not comparable. All of these have their places in the medical armamentarium. It would be a grievous mistake to disallow the usage of lututrin, as it would be to bar all those mentioned. There are no fetal abnormalities and no material side effects with lututrin.

I have used lututrin over the past 13 years and still have the satisfying belief that this medication delivers a good child to a household at times rather than one plagued by prematurity, and certainly one who faces a future of uncertain, but inevitable improprieties.

TABLE I.—*The effect of using lutrexin in the treatment of 75 multiparas*

Number of Cases	Before Treatment with Lutrexin		Total Live Births	After Treatment with Lutrexin
	Number of Previous Pregnancies	Total Pregnancies		Total Live Births
24	1	24	11	18
15	2	30	16	13
10	3	30	18	10
10	4	40	23	10
11	5	55	28	9
4	6	24	9	4
1	7	7	4	1
75		210	109	65

Chi Square for Above Data, 26.6; $P < .001$

TABLE II.—*A Resume of Thirteen (13) Primiparas Treated With Lutrexin Patients*

Case Number	*Description of Case*
1.	Ten years infertile—went into labor at six months—carried to term on Lutrexin.
2.	Bicornuate uterus—four successful pregnancies on Lutrexin. (This patient has now carried four pregnancies to completion with Lutrexin.)
3.	Bicornuate uterus—(first pregnancy carried on Lutrexin to term) (second pregnancy—no Lutrexin—delivered six weeks prematurely) (third pregnancy carried on Lutrexin to term)

TABLE II—Continued

Patients Case Number	Description of Case
4.	Sterility problem for six years. Placed on Lutrexin at 33 weeks. Delivered viable baby at 34 weeks.
5.	Carried four weeks on Lutrexin—viable baby.
6.	Placed on Lutrexin seven weeks prior to term—cervix dilated—sectioned one week before term.
7.	Twin pregnancy—carried 39 weeks to viability on Lutrexin.
8.	Early labor—placed on Lutrexin 38th week—viable baby at term.
9.	Early labor—placed on Lutrexin 35th week—carried to term.
10.	Ruptured membranes in second trimester—delivered at six months—dead fetus.
11.	Ruptured membranes at 36 weeks—delivered dead fetus at term.
12.	Went into labor at 24 weeks—carried to term on Lutrexin—viable baby.
13.	Early labor at three months—delivered a viable infant at term after being placed on Lutrexin.

REFERENCES

(1) Vital Statistics of the United States, Vol. 2 and Vol. 1, 1965, and final Mortality Statistics, 1966—Monthly Vital Statistics Report, Vol. 16, No. 12, Supplement March 12, 1968, H.E.W.

(2) Eastman, N. J.: Problems in the Evaluation of Obstetrics, JOURNAL AMA, *117*: 1293, 1959.

(3) Bishop, E. H. and Wouters, T. B.: Arrest of Premature Labor, JOURNAL AMA, *178*: 812, November 25, 1961.

(4) Sadusk, J. F., Jr.: The Definition of the Efficacy of a Drug Under the Law., THE BULLETIN, *5*:328–331, November–December 1964.

(5) Majewski, J. T. and Jennings, T.: A Uterine Relaxing Factor for Premature Labor., OBSTETRICS & GYNECOLOGY, *5*:649–652, May 1955.

(6) Majewski, J. T. and Jennings, T.: Further Experiences with a Uterine Relaxing Hormone in Premature Labor., OBSTETRICS & GYNECOLOGY, *9*: 322–325, March 1957.

(7) Rezek, G. H.: The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea., AMER. JOUR. OF OB. & GYN., *66*:396–402, August 1953.

(8) Jeremias, R. C. and Trythall, S. W.: "Uterine Incompetency" A New Concept in Mid-Pregnancy Abortion. Presented in Chicago at Soc. Fert. & Ster. Meeting, April 1962.

(9) Hoffmeister, F. J.; Schwartz, W. F.; Vondrak, B. F. and Martens, W.: Suture Reinforcement of the Incompetent Cervix., AMER. J. OBST. & GYN., *101*: 58–65, May 1, 1968.

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Date March 5, 1970.

*The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea**

(George H. Rezek, M.D., Cicero, Ill.)

The purpose of this paper is to report the favorable results secured in a series of clinical cases of dysmenorrhea with a new, nonsteroid, watersoluble uterine relaxing factor obtained from the corpus luteum.

In 1942 [1] we published the results of a clinical study of the value of Lutein in 650 cases of threatened and habitual abortion and other obstetrical complications involving the necessity of inhibiting uterine contractions. The favorable results obtained were shown to be due to the effectiveness of this product in inhibiting uterine contractions, as demonstrated by the intrauterine bag method of Moir.[2] When 10 c.c. of aqueous Lutein were injected into a patient whose uterine contractions had been stimulated by 1 c.c. of Pituitrin, there was complete cessation of contractions within twenty-five minutes. It was apparent from our study that this inhibition of contraction was not due to the progesterone content of the solution, and we suspected the presence of a heretofore unidentified substance. We drew attention also to the imperative need of further investigation of corpus luteum derivatives to determine the reason for the results which we had secured.

At that time there was no satisfactory laboratory method of standardizing substances derived from the corpus luteum except in terms of progesterone, which, in our experience, does not produce uterine relaxation. An intensive investigation, undertaken to devise a laboratory method of assaying the potency of these substances in terms of such relaxation, culminated in the development of a new technique for the determination of their effect on uterine activity, which was published by Krantz, Bryant, and Carr [3] in 1950.

New Uterine Relaxing Factor Assay

The new method of assay is based on the development and maintenance in the test animal of a uniform endocrine picture. This state was induced artificially in guinea pigs by injections of estrogenic material. One-tenth mg. of Diovocylin injected

*Presented at a meeting of the Chicago Gynecological Society, Jan. 16, 1953.
†Supplied by Hynson, Westcott & Dunning, Inc., Baltimore 1, Md.

subscutaneously into each animal daily for seven to twelve days before use caused proliferation of the uterus approximatey equal to that of a twenty-day pregnancy. In the conduct of the assay, the uterus is exposed through a midline abdominal incision, this organ then being attached to the writing lever of a kymograph. The jugular vein is also exposed for the purpose of making injections and the effect of such injections on uterine motility is observed by means of kymographic tracings.

A total of 26 different substances, including progesterone, were used with the idea of defining the specificity of the new factor in inhibiting uterine contractions. It was found that of these substances only the new uterine relaxing factor was effective. The test is, therefore, highly specific for this substance and is so extremely sensitive that 0.002 mg. produces definite relaxation.

The degree of relaxation of uterine contraction thus provides a direct method of assay of the potency of different samples of material obtained from the corpus luteum. Various methods of increasing this potency were devised and finally a highly active water-soluble nonsteroid substance was developed which inhibited uterine contractions when given by mouth as well as by injection.

A laboratory investigation reported by Hisaw and Frieden [4] at the Laurentian Conference on Hormones in Canada, September, 1952, establishes the fact that the uterine relaxing factor is a protein type of compound. It is interesting to note that still another ovarian substance was described by these investigators and their associates [5] at Harvard some years ago. This substance, which they have named relaxin, is closely related to the new uterine relaxing factor, but differs from it in that relaxin has the property of relaxing the symphysis pubis of the guinea pig. Further evidence that the two substances are not identical is provided by their electrophoresis curves.[6]

The effectiveness of the uterine relaxing factor in threatened and habitual abortion will be the subject of another paper.

Clinical Results

In view of the probable relationship between uterine contractions and dysemenorrhea it was decided to try the new potent substance orally in a series of clinical cases. This investigation was undertaken more than two years ago and to date a

total of 298 patients have been treated with highly satisfactory results. Seventy-two patients who responded well but who had also used a sedative were ruled out of this report.

For the purpose of clarity the clinical results will be divided into two series, the first treated by the original dosage schedule, and the second by a revised schedule.

FIRST SERIES

Seventy-three patients with a hyperplastic endometrium immediately before menstruation who used the new substance alone experienced relief from their cramps. Forty of these obtained excellent relief with 150 or 300 units every four hours. In this series the patients were observed for at least six periods and in some for as many as eleven periods. All were free from cramps and able to continue their daily routine, which they had been unable to do before use of the drug. Table I shows the number of periods observed in each of these cases.

TABLE I.—*Number of periods observed*

Periods	*Patients*
11	4
10	6
9	15
8	5
7	5
6	5

In another 20 cases the results can be described as good, in that patients were definitely better but did experience a few mild cramps. Each of these patients was observed for at least six periods. Fair results were obtained in 10 other cases. In this group the patients reported definite improvement but were still aware of menstrual cramps with some degree of pain. Only 3 stated that they had obtained no relief from the drug.

As a means of determining the elapsed time between the administration of the drug and relief of pain, 15 patients in the "excellent group" were asked to present themselves while having cramps and were given 450 units at once. Thirteen stated that within 15 minutes the cramps had almost completely disappeared. The other 2 had some improvement with the first dose and almost complete relief when an additional 300 units were given three hours later.

REPRESENTATIVE CASE HISTORIES

C. R., aged 23 years, had had dysmenorrhea every month since she was 13 years old. She had had over a period of 8 years, as she stated it, "all types of endocrine therapy." A dilatation and curettement and finally a presacral sympathectomy were carried out without relief of her menstrual cramps. This patient experienced relief from the uterine relaxing substance if she was able to take it before menstrual nausea and vomiting set in. When the periods started at night and she began vomiting, she was unable to take tablets, but if the period began during the day and tablets were taken in time she received complete relief from her uterine cramps.

R. R., aged 28 years, had had dysmenorrhea since the birth of her second baby 4 years ago. Excellent results were experienced with 150 units every 4 hours.

K. D. aged 19 years, had had cramps since the onset of the menses at the age of 14 years. No previous therapy had been used, but she reported excellent results with 150 units every 4 hours.

M. P., aged 16 years, was a virgin and no endometrial biopsy was performed. She had had cramps since the onset of the menses at the age of 12, but received excellent results with 300 units every 4 hours. Rectal examination revealed no pelvic pathology.

A. B., aged 19 years, had had dysmenorrhea for the past 4 years. The menses started at the age of 13 and the first 2 years were pain free. There was no pelvic pathology. She received excellent results with 150 units every 4 hours.

R. H., aged 33 years, was a nullipara. The menses started at the age of 14 years; the first 10 years were without dysmenorrhea, but during the last 9 years, she has had severe dysmenorrhea. Pelvic examination revealed the patient to have bilateral salpingitis. Three hundred units of the drug every 4 hours gave excellent results in relieving cramps.

In the group with hypoplastic endometrium immediately premenstrually there were 10 patients; only 2 claimed some relief and 8 said they experienced no relief.

SECOND SERIES

It was our impression at this time that, in general, patients responded more rapidly to the larger doses. In some instances

relief with dosages up to 450 units was not secured until the second, third, or fourth dose. We had seen no evience whatsoever of untoward reaction and, in view of the fact that other investigators had used much larger doses experimentally, we decided to give an initial dose of 1,500 to 3,000 units. Patients in the second series received an average of 2,300 units initially. With this regimen we found that relief of pain was secured within approximately 15 minutes. Furthermore, in some cases only one dose was required for any given period.

Fifty-eight patients with normal endometrium were treated in this way and of these 40 experienced complete relief of pain within fifteen minutes. Of 10 other patients with hypoplastic endometrium 3 experienced relief with a dose of 3,000 units. It is apparent, therefore, that the larger dosage is more effective and that patients with a normal endometrium respond more readily and frequently than those with a hypoplastic endometrium. In this series patients were observed for at least three periods.

[Figures 1 and 2 omitted.]

A further observation in this series was that in a number of instances patients who suffered regularly from painful periods experienced no such symptoms for several periods following the use of 3,000 units of the uterine relaxing factor. The number of patients reporting relief for more than one period following a single large dose is not, however, sufficiently large to permit any definite conclusions.

Laboratory Confirmation

Since the guinea pig uterus relaxation test had been found to be highly specific for the new substance, it was decided, as an additional check on the absorption of the drug, to take blood samples from patients who had received it and to test them by the above method. As a control, samples of the patients' blood were also taken before administration of the drug. It was found that, although control samples produced no effect in inhibiting uterine contractions, specimens taken thirty minutes after administration produced a characteristic relaxation of the guinea pig uterus. This is illustrated in Figs. 1 and 2 which are reproductions of typical kymographic tracings secured before and after administration of the uterine relaxing factor in a total of 25 patients to date.

Summary

1. The highly favorable results in a series of 298 clinical cases of dysmenorrhea treated with a new potent uterine relaxing factor of the corpus luteum are described.

2. Complete relief was secured within fifteen minutes in approximately 70 per cent of patients with normal endometrium when treated with an initial dose of 3,000 units.

3. Response to the smaller initial dose used in the first series was not quite as satisfactory, demonstrating the need of a large first dose.

4. Patients with a hypoplastic endometrium appeared to respond less well.

5. No undesirable by-effects of any kind were noticed, although some patients were observed for as long as 11 periods.

6. All patients who responded were able to continue their daily routine, which they had previously been unable to do.

7. The suggested dosage for the new uterine relaxing factor is 1,500 to 3,000 units at the beginning of pain. In many cases no further drug is required for that period.

8. Absorption of the drug into the blood stream was confirmed by laboratory procedures.

Conclusion

In our experience the new uterine relaxing factor described above is effective in the relief of menstrual pain.

References

1. Falls, Frederick H., Rezek, George H., and Benensohn, S. J.: Surg., Gynec. & Obst. 75: 289, 1942.
2. Moir, Chassar: Brit. M. J. 1: 1022, 1932.
3. Krantz, J. C., Bryant, H. H., and Carr, C. J.: Surg., Gynec. & Obst. 90: 372, 1950.
4. Frieden, E. H., and Hisaw, F. L.: Arch. Biochem. 29: 166, 1950.
   Frieden, E. H.: Arch. Biochem. 30: 138, 1951.
   Frieden, E. H.: Fed. Proc. 10: 184, 1951.
   Frieden, E. H., et al.: Laurentian Conference Report. In press.
5. Hisaw, F. L., and Zarrow, M. X.: In Vitamins and Hormones, Vol. 8, Academic Press, N.Y., 170, 1950.
6. Felton, Lloyd C., Frieden, Edward H., and Bryant, Harold H.: J. Pharmacol. & Exper. Therap. 107: 160, 1953.

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The undersigned hereby certifies that the foregoing is a true and correct copy of his paper entitled *The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luteum in the Treatment of Dysmenorrhea*, which appeared in the American Journal of Obstetrics and Gynecology, Vol. 66, No. 2, p. 396, August, 1953.

GEORGE H. REZEK, M.D.

Date March 5, 1970.

Lutrexin in the Treatment of Premature Labor

(By G. H. Rezek, University of Illinois College of Medicine, Chicago, Ill.)

Since 1903, when Ludwig Frankel of Breslau showed that the removal of the corpus luteum in the pregnant rabbit caused it to abort, there has been a more or less constant search by many investigators to find a substance in the corpus luteum or ovary that could be used in the treatment of habitual and threatened abortion and premature labor. Since the paper by Krohn *et al.*,[1] there have been many papers that have shown that various extracts of the corpus luteum are of value in the treatment of threatened abortion and premature labor. In 1942 Falls *et al.*[2] showed relatively good results in over 600 cases with an injectable corpus luteum extract. In 1950 Krantz *et al.*[3] showed that an aqueous extract of the sow corpus luteum had the ability to diminish uterine tone and abolish contractions of the guinea pig uterus in situ. I [4] used the same material to determine its effectiveness in the treatment of dysmenorrhea. Jones and Smith [5] also used the substance in the treatment of dysmenorrhea. Majewski and Jennings (6a), (6b) continued the work with this substance in the treatment of clinically diagnosed cases of premature labor. It is my belief that threatened abortion differs from premature labor only in the length of gestation. Threatened abortion presents a problem in differentiating between a true threatened abortion and an incomplete abortion while, in premature labor, it is difficult to differentiate between premature labor and normal Braxton Hicks contractions. Because many different etiological factors may cause the premature emptying of the uterus, one can expect difficulty in finding one type of treatment to take care of all the factors. All the theories as to the mechanics of the onset of labor are

hypothetical. Some feel that the increasing size of the uterus may cause growing irritability and produce spontaneous labor. Other theories are concerned with the environment of the cervix and lower uterine segment of the uterus near term, the carbon dioxide content of the blood, and senility of the placenta. Lash and Lash [7] feel that the incompetent os is a factor in premature labor, and Trythall [8] has achieved 55 per cent good results with the use of Lutrexin in the treatment of the incompetent os. Others feel that psychic or physical trauma may be the trigger mechanism that produces premature labor. Since Snyder [9] has been able to prolong the duration of pregnancy in the rabbit by inducing ovulation near term, and since Heckel and Allen [10] have used progesterone to delay parturition of the rabbit, the hormonal initiation of labor probably is a good factor.

In this series of 54 cases of premature labor between 24 and 34 weeks' gestation treated with Lutrexin, the presence of at least 2 of the following 4 conditions was necessary for classification as premature labor: (1) regular uterine contractions causing definite discomfort to the patient; (2) at least 2-cm. cervical dilatation in a primipara and at least 3-cm. dilatation in a multipara; (3) some vaginal bleeding or a bloody show; and (4) rupture of the bag of water. Uterine contractions with progressive descent of the head but without cervical dilatation or bleeding were considered normal Braxton Hicks contractions and were not included in this series of 54 cases.

The treatment consisted of bed, rest plus 3000 units of Lutrexin* orally every hour until the symptoms subsided, and then 3000 units 4 times a day for 2 days. After this the patient was permitted to be up, and received 1000 units 3 times a day until viability was reached (36 weeks). The patient was not awakened at night for therapy. In 36 of the 54 cases the patient was given a barbiturate at night for sleep; no sedation was used in the daytime except in 6 quite disturbed cases that required tranquillizers.

On the 54 cases, there were 14 failures; of these 14 failures, 2 fetuses survived—one weighed 3 lb. 14 oz., and one weighted 2 lb. 15 oz. In the 12 that did not survive the weight varied from 1 lb. 12 oz. to 3 lb. 15 oz. Two were stillborn. A case was classified as a failure if the patient continued to have pains and terminated the pregnancy. The 40 that were classified as suc-

*Hynson, Westcott & Dunning, Inc., Baltimore, Md.

cesses continued with the pregnancy for at least an additional 28 days. In the group of failures, 4 were first seen with 4-cm. dilatation and ruptured membranes, and all terminated their pregnancies in less than 12 hours. In the salvage group of 40 cases, 5 had ruptured membranes, but with very little dilatation of the cervix (less than 2 cm). Thirteen patients of this series had been hospitalized previously as cases of threatened abortion between the tenth and sixteenth weeks of gestation. Four of the 54 cases proved to be cases of placenta praevia that began to bleed between 24 and 27 weeks. Diagnosis of placenta praevia was confirmed at the time of cesarean section between 36 and 38 weeks. One case of placenta praevia threatened to abort at 14 weeks and again at 19 weeks. In this series there were 30 primiparas and 24 multiparas. Of the 54 cases, 32 had lost at least 1 pregnancy and 2 had lost 3.

SUMMARY

In this series of 54 cases, premature labor was stopped in 40 cases (74 per cent) for at least 28 days. I feel that, by delaying delivery for 28 days or more, we have enabled many fetuses to survive that otherwise would have died because of prematurity.

It appears that the substance that inhibits uterine contractions and is of value in the treatment of premature labor, threatened abortion, and dysmenorrhea has not been completely isolated, but is found in Lutrexin in therapeutic amounts.

There were no untoward effects noted from this therapy.

REFERENCES

1. Krohn, L., F. H. Falls & J. A. Lackner. 1935. Am. J. Obstet. Gynecol. 29: 198.
2. Falls, F. H., G. H. Rezek & S. Benensohn. 1942. Surg. Gynecol. Obstet. 75: 289–299.
3. Krantz, J. C., Jr., H. H. Bryant & C. J. Carr. 1950. Surg. Gynecol. Obstet. 90: 372.
4. Rezek, G. H. 1953. Am. J. Obstet. Gynecol. 66(2): 396–402.
5. Jones, G. S. & F. Smith. 1954. Am. J. Obstet. Gynecol. 67: 628.
6a. Majewski, J. T. & T. Jennings, 1955. Obstet. & Gynecol. 6: 649.
6b. Majewski, J. T. & T. Jennings, 1957. Obstet. & Gynecol. 9: 322.
7. Lash, A. F. & S. R. Lash, 1954. Habitual abortion: the incompetent internal os of the cervix. Am. J. Obstet. Gynecol. 59: 68–74.
8. Trythall, S. W. 1957. Congenital inadequacy of the cervix. Am. Soc. for the Study of Sterility, New York, N.Y.
9. Snyder, F. F. 1934. Prolongation of pregnancy and complications of parturition in the rabbit following induction of ovulation near term. Bull. Johns Hopkins Hosp. 54: 78.
10. Heckel, G. P. & W. M. Allen. 1938. J. Obstet. Gynecol. 35: 131.

The undersigned hereby certifies that the foregoing is a true and correct copy of his paper entitled *Lutrexin in the Treatment of Premature Labor* which appeared in the Annals of the New York Academy of Sciences, Vol. 75, Art. 2, p. 995, January 1959.

GEORGE HENRY REZEK, M.D.

Date: March 5, 1970.

ARTICLES

*The Use of Progestational Agents in Pregnancy**

(Willard M. Allen, MD, St. Louis, Missouri)

There are many approaches to the treatment of habitual abortion. This paper presents a logical method substantiated by a convincing clinical study.

The advent of the newer progestational agents has raised again the question of the presumed value of progesterone and related compounds in complications of pregnancy, such as threatened abortion, habitual abortion and premature labor. The physician today is confronted with a decision as to which one of the many compounds should be used and with the question of safety as well as effectiveness. Some physicians are therapeutic nihilists, others are enthusiasts for hormone therapy, others for psychotherapy and still others for vitamin therapy. With such divergent methods of treating these conditions it seems evident that no uniformly satisfactory method has been reached.

There is little disagreement regarding the need for some method for preventing premature labor. Prematurity takes a dreadful toll among newborn infants. If the premature survives there is apt to be great expense in the raising of the premature in addition to the apprehension concerning the future health of the child. A whole specialty has been developed by the Pediatricians to care for these tiny newborns, yet preciously little has been accomplished as yet to prevent the premature birth of babies, the majority of which are surely normal babies who would have had a much better chance for life had they been born at or near term.

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* Presented at 61st Annual Meeting of the Wyoming State Medical Society, Sept. 1964. From the Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, Mo.

The problem of early abortion is equally challenging although not quite so devastating to the family as premature labor. Habitual abortion, on the other hand, is a serious situation which creates many family problems.

Threatened abortion is an ever present problem to the physician who does obstetrics. Probably one pregnancy in ten results in abortion. Many of these are "blighted" and the abortion is Nature's method of ridding the patient of an abnormal fetus. Various explanations for the blighted pregnancy are given, such as late fertilization of the ovum, an inadequate progestational endometrium resulting in poor placentation, nutritional deficiencies, etc. The therapeutic nihilist insists that nothing should be done to discourage abortion because the fetus is abnormal anyway. However, I do not believe that we can take the view that a fetus which is abnormal at the time of abortion was necessarily abnormal from the time of conception or even from the time of implantation. One only has to recall the thalidomide tragedy to realize that supposedly safe drugs can have a catastrophic effect when given at a critical period in early pregnancy. Also we need to remind ourselves that excessive amounts of both estrogens and androgens, or certain vitamin deficiencies in early pregnancy in certain animals can destroy the pregnancy. Some of the abnormal fetuses which result in abortion may be man-made although not necessarily physician-induced.

The desirability of treatment of a threatened abortion is obviously open to some question. However, if one elects to treat such a patient a pelvic examination should surely be done. In many cases the uterus is smaller than expected. Such patients should not receive hormone therapy. We have seen numerous patients in which the abortion of an abnormal pregnancy has been delayed for weeks, or even months, by the use of progestational agents. On the other hand, if the uterus is soft and enlarged to the expected degree, the use of progestational agents may save the pregnancy. It is, of course, difficult to prove statistically that hormone therapy does save the pregnancy as there are many pregnancies in which bleeding and cramping occur yet the pregnancy proceeds normally with no therapy other than rest in bed. This fact makes it imperative that the

progestational agent be safe even though its effectiveness in threatened abortion can not be proved beyond question.

Discovery of Progesterone

With this introduction, half philosophical, I will proceed to a brief discussion of progesterone and the newer progestational agents. The presumed effectiveness of progestational agents is based on the concept that a deficiency of progesterone may be responsible for abortion and premature labor. This concept did not originate from any knowledge which we have of hormonal deficiency in human pregnancy, but rather from extensive studies in animals which, in fact, led to the discovery of progesterone itself. These studies occurred so long ago that the current house-officers or young physicians know about them only by hearsay, yet they are not truly ancient, as I was an active participant in them. In many laboratory animals, removal of the ovaries during pregnancy results in abortion or premature delivery. The pregnancy terminates because of removal of the source of progesterone, namely the ovaries. Furthermore, the administration of progesterone (or in some animals, estrogen plus progesterone) permits the pregnancy to progress normally despite removal of the ovaries. However, for such animals to deliver, it was necessary to discontinue the progesterone, a fact which was further substantiated by the observation that parturition in normal animals could be delayed or even prevented entirely by the administration of progesterone.

It was, of course, easy to convert these extraordinarily valuable facts regarding animals to the concept that progesterone should be a cure-all for abortion and premature labor in the woman. Unfortunately, measurements of urinary pregnanediol and blood progesterone in human pregnancy give little or no firm indication of progesterone deficiency immediately prior to either term or premature labor. The fact still remains, however, that both pregnanediol and estrogen disappear from the urine within a few days following delivery of the fetus and placenta. Actual studies in human pregnancy, therefore, give little support to the concept. On the other hand, there is abundant evidence that the same hormones are being produced throughout human pregnancy as are produced in animals. These naturally

produced hormones must be essential to the successful completion of pregnancy yet their exact role or significance in parturition or premature labor remains obscure. This is rather disturbing when we realize that progesterone, estrogen and chorionic gonadotropin were discovered over 30 years ago, and their biological effects in animals were for the most part reasonably well clarified prior to 1940.

The use of progesterone and progestational agents in human pregnancy is, therefore, based on the unproved assumption that progesterone deficiency is responsible for threatened and habitual abortion, and premature labor. The information available from the medical literature does indicate that progestational agents are beneficial but I should emphasize that the results are not based on any clear-cut evidence of progesterone deficiency. There is no need, therefore, of using any laboratory test for pregnanediol as a requirement for therapy.

EVIDENCE OF USEFULNESS

I would like, now, to give you some of the evidence which substantiates progestational agents as useful drugs in the treatment of habitual abortion and premature labor. I will present first the results of my own experience on 20 private patients, all referred to me because of the problem. The most obvious fact is that these 20 women had experienced 80 pregnancies with only 10 living chilrden prior to the pregnancy treated with the progestational agent. This proves beyond doubt that this group is made up of patients with some serious disorder leading to poor obstetrical performance. No obvious cause was responsible, no patient had hypertension or kidney disease, and only one patient was known to have a congenital malformation of the uterus (only two patients had the Shirodkar operation as an adjunct to hormone therapy). There may be some question as to the desirability of treating patients who have had only two consecutive losses prior to the treated pregnancy. In actual fact, there were only two patients in the group who had lost but two pregnancies prior to the treated pregnancy. One of these had lost two normal children at 5½ months from prematurity and the other patient had two abortions at 3½ months with normally developed fetuses (Table 1).

TABLE 1.—*Fetal salvage in cases with two consecutive abortions immediately preceding pregnancy treated with progestational agent*

	Treated Pregnancy	All Previous Pregnancies
Total No.	20	80
Full term, survived	14	8
Premature, survived	4	2
Premature, died	0	19
Missed Abortion	1	4
Early Abortion	1	47
Success Rate	18/20(90%)	10/80(12.5%)

The next obvious fact is that in the first pregnancy treated with the progestational agent, 18 living children survived, four of which were born prematurely. In the great majority of these pregnancies the progestational agent was begun as soon as the pregnancy was definitely established and usually about two weeks after the period was missed. These cases were not actually all treated with the same hormone. Two cases were given 50 mg. progesterone i.m. daily, two cases received 100 mg. progesterone sublingually daily, one case received Pranone, and 15 cases received Delalutin, 125–250 mg. two or more times weekly. There was one early abortion in the 20 pregnancies. This is about the expected incidence. The premature rate of 20 per cent is somewhat higher than expected. Actually, the rate is virtually the same as in the previous untreated pregnancies in the group. However, in the previous pregnancies only 2 or 21 prematures survived, whereas all 4 of the prematures in the treated pregnancies were sufficiently mature to survive. These results, surely, indicate that the treated pregnancy gave a measure of family happiness not experienced from the previous pregnancies.

According to Malpas, after one abortion the success rate in the next pregnancy is 78 per cent, after two consecutive abortions, 62 per cent, after three consecutive abortions, 27 per cent, and after four the chance of success in the next pregnancy is reduced to 8 per cent. These figures surely indicate that repeated abortions, especially after three consecutive abortions, reduces the probability of a successful pregnancy to a very discouraging level. Correspondingly, these figures lend considerable credence

to the belief that therapy is beneficial when a high percentage of pregnancies are saved.

In this series the histories were sufficiently reliable to tabulate the success rate in relation to the order of the pregnancy. In the very first pregnancy these 20 women had 6 living children. At the end of the first 40 pregnancies (i.e. 2 pregnancies per subject) there were only 7 living children, and at the end of the first 55 pregnancies (2 or 3 per subject) there were only 10 living children. These patients, therefore, showed no tendency to secure better fetal salvage as they had more pregnancies. The spontaneous "cure-rate" in this group, therefore, was not apparent (Table 2).

TABLE 2.—*Fetal salvage prior to treated pregnancy, 20 cases*

Order of Pregnancy	1	2	3	4	5	6	7	8	9	Totals
Term Survivors	6		2							8
Premature Survivors		1	1							2
Premature Died	3	4	2	4	4	2				19
Missed Abortions		1	2			1				
Abortions	11	14	8	7	2	1	2	1	1	47
Total	20	20	15	11	6	4	2	1	1	80
Percent Survival	30	5	20	0	0	0	0	0	0	12.5

The successful accomplishment of a pregnancy in patients with such a dismal history inevitably raises questions regarding the management of the next pregnancy. The patient obviously wants the next pregnancy managed in the same way as the successful pregnancy. The physician seldom has the opportunity to omit treatment and thereby secure a "control." This series is no exception. There were 24 pregnancies in this group after the first pregnancy treated with the progestational agent. In 18 of these the progestational agent was used. There were 16 term or near term normal children born (success rate 89 percent). In the 6 untreated pregnancies, 4 normal living children were born and 2 pregnancies resulted in prematures that failed to survive (success rate 67 percent). While little significance can be given such small numbers, it would appear that the salvage rate in untreated pregnancies, even after the successful completion of one or more pregnancies with therapy, is perhaps below the expected (Table 3).

TABLE 3.—*Fetal salvage in pregnancies subsequent to first pregnancy treated with progestational agent*

	Treated	Untreated
Total No.	18	6
Full term, survived	15	4
Premature, survived	1	----
Premature, died	1	2
Early Abortion	1	----
Success Rate	16/18(89%)	4/6(67%)

At this point I presume most of you have concluded that I have over-emphasized the good results in the small series of cases, but if you have, your conclusion is premature. There are other studies which are reliable and which are in agreement with my own. In 1957 [4] Davis and Plotz reported their results in the treatment of 90 cases of habitual abortion with intramuscular progesterone. The fetal salvage in pregnancies prior to the treated pregnancy was 13.8 per cent and in the treated pregnancy 69.7 per cent. The next year Reifenstein compiled the results of treating 89 cases of habitual abortion with Delalutin. In his group of cases the salvage prior to the treated pregnancy was 13.4 per cent and in the treated pregnancy 70 per cent. Boschann [3] likewise has reported his results in 12 cases of habitual abortion (three consecutive abortions immediately preceding the treated pregnancy). The success rate prior to the treated pregnancy was 21 per cent and in the treated pregnancy 67 per cent. My own cases are in accord with these results.

I think it is quite proper to conclude that both progesterone and Delalutin are effective agents in the treatment of habitual abortion. Also, it is well known from these studies that the female infants were not masculinized at birth despite large doses of either progesterone or Delalutin beginning very early in pregnancy. It is proper, therefore, to also conclude that these hormones are safe.

There is a good deal of uncertainty regarding what type of study should be carried out in order to fully establish the validity of the results. In these studies the patient herself serves as the control; the results in the pregnancies prior to the treated pregnancy are compared with the results in the treated pregnancy. A supposedly better method of study which is popular

today would utilize the placebo method; one patient receives the hormone and the next patient the placebo, the investigator not knowing which patient received the placebo until the study is complete. This type of study is now so "sacred" that any other type is often not recognized as investigative. However, there are many clinical problems in which this type of study violates the rules of clinical morality as well as common sense. Let us consider some disease in which the risk of death is appreciable, lobar pneumonia, for example. No clinician could risk treating alternate cases with an antibiotic and a placebo. In such a study the risk of death while receiving the placebo might be as much as 25 per cent. In the study of habitual abortion the risk of death to the fetus in utero is between 80 to 90 per cent. It seems to me that one no longer has the right to use a placebo as a control because the data already available from the studies in which the patient serves as her own control indicate that the fetal losses are reduced from 80 or 90 per cent to 25 per cent or perhaps less.

The contrasting point of view has been eloquently presented by Goldzieber.[6] He rejects the idea that a patient can serve as her own control. He points out quite properly that the solicitous help of the physician may exert a beneficial effect and gives data to indicate that equally good results in habitual abortion have been reported from various types of therepy which could scarcely be called specific. Javert[7] is of the same opinion. These contrary opinions do not, of course, alter in any way the results which have been obtained and are here reported; the interpretation of the results may vary but the observations are facts.

I have presented these aspects of the problem to emphasize that I believe drugs should not be eliminated from the armamentarium of physicians because their effectiveness may not have been proved beyond all possibility of doubt. New drugs should be as safe as possible, but even safety of an effective drug can never be fully guaranteed. Safety and effectiveness are words like good and evil. Their meaning is always related to something such as the seriousness of the disease, the magnitude of the crime or the mores of society.

The objection of Goldzieber[5] to using the patient as her control may be partially met by a recently reported study by LeVine.[8] He has compared the effect of a placebo and Dela-

lutin in 30 cases of habitual abortion. One half of the patients received 250 mgm. of Delalutin twice weekly and the other half received a placebo injection. The success rate was 73 per cent in the patients receiving the hormone and 42 per cent in the controls.

The data I have presented to this point deal with the use of two compounds, progesterone and Delalutin. To be effective these compounds must be given by intramuscular injection. Delalutin is the caproate ester of 17-hydroxy-progesterone. So far as we know, this compound has all of the properties of natural progesterone. It has the distinct advantage of being much more soluble in sesame oil and is also somewhat more prolonged in action. This hormone has, therefore, replaced progesterone for use during pregnancy where large doses over a long period of time are necessary.

The advent of orally effective progestational agents has, of course, introduced a new approach to the problem. Enovid, Orthonovum, Norlutin, Dufaston, Norinyl, Provera, and Provest are all orally active progestational agents, each being able to produce a progestational endometrium in the woman. They are, therefore, potentially useful in theory at least. Enovid, Orthonovum, Norinyl and Provest all contain added estrogen. This estrogen is added to enhance their capacity to suppress ovulation. The added estrogen would not necessarily reduce their usefulness during pregnancy. These compounds are not utilized as a rule because they contain only small amounts of the progestational agent.

The effectiveness of Provera and Norlutin, orally active progestational agents, has not been as fully established, in my opinion, as has the effectiveness of Delalutin and progesterone. However, the data available suggest that some of these preparations may be useful. Literally thousands of cases of threatened abortion have received Provera and Depoprovera. As I mentioned earlier, it is difficult, if not impossible, to prove effectiveness beyond doubt in threatened abortion. No extensive series of habitual abortions has been reported with Provera. However, Berard [2] has recently reported his results in treatment of threatened abortion and habitual abortion. In his cases there were 11 who were habitual aborters. In the pregnancy treated with Provera (orally, 10–30 mgm. daily) 10 living

fetuses were delivered at or near term. This small series, therefore, tends to indicate that oral Provera may be as effective as intramuscular Delalutin or progesterone.

The differences of opinion regarding the effectiveness of progestational agents in human pregnancy are unlikely to be resolved in the near future. There is no simple way of inducing progesterone deficiency in the pregnant woman nor does Nature, herself, provide us with any disorders in which there is clear cut progesterone deficiency. The problem is infinitely more complicated in the woman than it is in the pregnant rabbit where progesterone deficiency can be deliberately induced by ovariectomy during pregnancy. In this animal, progesterone, Delalution [10] and Provera [11] supplement perfectly for the deficiency of progesterone induced by ovariectomy but Norlutin [1] does not. Until methods are evolved which will diagnose progesterone deficiency before irreparable damage to the pregnancy has occurred clinical methods such as have been reported will have to suffice as evidence regarding their effectiveness.

SUMMARY

A series of 20 cases of habitual abortion treated with progesterone or Delalutin is reported. These 20 women experienced 80 pregnancies with only 10 living children (12.5 percent) before they entered the study. In the first treated pregnancy 18 children (90 percent) survived. These results are in accord with other series reported in the literature.

REFERENCES

1. Allen, W. M. and Wu, D. H.: Fert. & Sterility 10:424 (1959).
2. Berard, M. J.: Canad. Med. Assoc. J. 91:212 (1964).
3. Boschann, H. W.: Ann. New York Acad. Science 71:727 (1958).
4. Davis, M. E. and Plotz, E. J.: Recent Progress in Hormone Research XIII:347 (1957).
5. Goldzieher, J. W.: Ann. New York Acad. Science 71:783 (1958).
6. Goldzieher, J. W.: Med. Clin. North America 48:529 (1964).
7. Javert, C. T.: Obst. and Gynec. 3:420 (1954).
8. Le Vine, L.: West. J. Surg. Obst. and Gynec. 72:30 (1964).
9. Reifenstein, E. C.: Ann. New York Acad. Science 71:762 (1958).
10. Wu, D. H. and Allen, W. M.: Fert. & Sterility 10:439 (1959).
11. Wu, D. H.: Fert. & Sterility 12:236 (1961).

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OBSTETRICS AND GYNECOLOGY

Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases.

The maintenance of the state of pregnancy as close to full term as possible is generally a prime consideration in the delivery of a viable baby. In my obstetrical practice, I have employed Lutrexin in the management of cases of premature labor, threatened abortion and habitual abortion for the past fifteen years and a review of my records of the last three years reveals about 86% success in the treatment of such cases. The following description of fifteen recent representative cases reveals the effectiveness of Lutrexin in the treatment of these allied conditions.

In six patients (No. 1, 3, 5, 6, 10 and 15), there were histories of miscarriage, premature deliveries and abortion prior to presentation at my office for care. In twelve earlier pregnancies, there were only two live births. With the use of Lutrexin in these patients, covering from one to four pregnancies, there were eleven live births and no deaths.

Five patients (No. 7, 8, 9, 12 and 14) did not have prior histories of miscarriages, abortions or prematurity when first seen. Most of these patients were generally characterized by cramps, but with the use of Lutrexin during all of their pregnancies, they delivered a total of eleven healthy babies over as little as one to as many as five pregnancies.

In the remaining four patients (#2, 4, 11 and 13), it is of interest to note that patient # 2 delivered viable babies during her first and third pregnancies when Lutrexin was used, but had a miscarriage during the second pregnancy when the drug was not employed. Patient No. 4 showed one failure and one success with Lutrexin therapy. Patient No. 5 in five pregnancies delivered four viable and one dead baby. Patient No. 13, with the help of Lutrexin, delivered viable babies in three of her pregnancies: during her fourth pregnancy when this treatment was not administered, a spontaneous abortion occurred.

If the five patients (# 7, 8, 9, 12 and 14) who did not have any prior history of miscarriages, etc. are excluded (although my experience indicates that in many instances such cases when not treated with Lutrexin are less likely to deliver viable babies), then in the remaining ten cases when Lutrexin was not used, there were only four live births out of eigtheen pregnancies; when Lutrexin was used, there were twenty-one live births out of twenty-three pregnancies. This difference is highly significant, P= .001.

To summarize, for over fifteen years I have found Lutrexin to be a most useful drug in the treatment of premature labor and threatened and habitual abortion, with a successful rate of about 86%. Side effects with Lutrexin have never been noted in studies or in my practice.

Sincerely,

(S) Fred B. Gray, M.D.
FRED B. GRAY, M.D.

FBG:ch

FRED B. GRAY, M.D.,
456 Cherry Street, S.E.
Grand Rapids 3, Mich.

RESUME OF CASES TREATED BY LUTREXIN FOR PREMATURE LABOR, THREATENED ABORTIONS AND HABITUAL ABORTIONS

OBSTRETRICS AND GYNECOLOGY

Cases

1 1. A 22 year old WF came to my office 5 months after she had a miscarriage at 6 weeks gestation. She was five weeks pregnant and cramping. I put her on Lutrexin at once and gave her progesterones IM and sedatives when the cramping was complicated with spotting. She had a normal fast delivery on August 15, 1968 at term.

2 2. This 22 year old WF was treated with Lutrexin and progesterones throughout her first pregnancy and had a normal delivery at 38 weeks gestation. I was out of town early in her second pregnancy. She did not receive any Lutrexin and had a miscarriage at six weeks gestation. Early in her third pregnancy she began cramping and spotting. She was given progesterones along with Lu-

Cases

trexin as long as the spotting continued and then carried along on Lutrexin only. She was delivered of a viable baby at 36 weeks gestation.

2 3. This girl came to me at the age of 27 after having 3 premature deliveries and two dead and one live baby. She was eight weeks pregnant when she came in and was cramping severely. She was placed on a Luxtrexin schedule and was delivered of a viable baby at 8 months gestation.

Three years later she came in again with the same problem and was given the same treatment. She maintained her pregnancy for 39 weeks and was delivered of a healthy infant.

3 4. This 35 year old WF had two normal deliveries and one spontaneous abortion in Detroit. Five years later she came to me when she was twelve weeks pregnant. She was cramping and was put on the Lutrexin schedule along with bed rest. In spite of all efforts, she had a spontaneous abortion at 16 weeks gestation. Four months later she was pregnant again with the usual cramping. At four months gestation the fetal heart could not be heard and she had a prolapsed cord. She had a miscarriage and D & C. Two years later she was pregnant again and was given Lutrexin at once and continued throughout her pregnancy. She maintained this pregnancy for 39 weeks when a low cervical Caesarian section was done because of a transverse lie. The baby was healthy although there was a lot of meconium in the amniotic fluid.

2 5. This 35 year old WF had had an abortion at 4 months gestation in Oct. 1957, another miscarriage at 5 months gestation in August 1958 and another at 6 months gestation in December 1959. She came to me in June of 1965 at ten weeks gestation. She was immediately started on the Lutrexin regime and was delivered of a healthy baby at term. In October of 1967 she was placed on Lutrexin beginning in the eighth week of her pregnancy. She was delivered of a 7 pound 12½ ounce infant at term.

4 6. This young lady had two spontaneous abortions in her first pregnancies. In her subsequent four pregnancies she was placed on Lutrexin whenever she started cramping and kept on it until the cramping abated. She had four normal deliveries at term.

Cases

3 7. This patient was kept on Lutrexin throughout three pregnancies and was delivered of three healthy infants—two at term and one at 36 weeks gestation. Her membranes ruptured at 34 weeks when she was admitted to the hospital under careful surveillance and on Lutrexin.

1 8. This 28 year old WF had a relatively normal pregnancy until 34 weeks gestation when she began cramping. She was kept on Lutrexin and was delivered at term.

5 9. This young lady was a problem. She had cramps from 24 weeks on through 5 pregnancies which was complicated with marginal bleeding in the latter stages. Her pregnancies were maintained with the help of Lutrexin through 37 to 39 weeks and has 5 healthy youngsters.

1 10. This 23 year old lady had a normal delivery in 1962. On March 2, 1965 she had a sudden, spontaneous abortion at ten weeks gestation before she had any prenatal care. In July of 1965 she came to my office at 7 weeks gestation. At twelve weeks, she began cramping and was placed on Lutrexin and kept on it until delivery at 39 weeks. She is 22 weeks pregnant at the present time and to date she has had no problem but in the event she begins cramping, she will be put on the Lutrexin regime.

5 11. This young lady was and is also quite a problem. She has had five pregnancies and was on Lutrexin throughout each one. She had one full term delivery, 1 abortion at 5 months gestation and 3 premature deliveries. In three of her pregnancies the cramping was complicated with spotting which was controlled with progesterones. She has four healthy children which I firmly believe she would not have without the help of Lutrexin. Several times she was taking 2 Lutrexin tablets around the clock (every three hours). She said she did not need an alarm clock as when the medication started to wear off, the cramps would awaken her and would be relieved shortly after taking the Lutrexin.

1 12. This 30 year old white female began cramping at 16 weeks gestation and was given Lutrexin whenever she needed it until she delivered at 39 weeks.

3 13. This young lady had four pregnancies. She cramped throughout three of them and maintained her pregnan-

Cases

cies for 38 weeks with the help of Lutrexin. Her fourth pregnancy was terminated at nine weeks by a spontaneous abortion. She had had no prenatal care. I was on vacation at the time.

1 14. This patient (age 27) had the complication of fibroids in the uterus when she became pregnant in early 1966. Her pregnancy followed a rocky course but with the help of Lutrexin and TLC she delivered at 38 weeks. She has a healthy boy. I performed a myomectomy on her in July of this year and we are hoping she will have future successful pregnancies.

1 15. This 24 year old WF had a miscarriage in Brighton in 1966 at 3 months gestation. She come to me in November 1967 at 6½ weeks gestation. She was already cramping and was started on Lutrexin. She leveled off and at 24 weeks she was taking it only when she started cramping. She was delivered of a viable infant at 38 weeks gestation.

I hope this resume will prove helpful to you.

Sincerely,

(S) Fred B. Gray, M.D.
FRED B. GRAY, M.D.

FBG:ch

There are others—2 have twins at Butterworth Hospital now at 34 wks and she was 4 cm. dil. and contr. every 4 min. 45 sec. She had been on Lutrexin 2 qid. This was stepped up to 4 tabs every hour for 4 hrs. qid. and she is now 36 wks and her cervix is 2 cm. dil. I have x-rays of twins and hosp. confirmation of her treatment. The drug is routine at our hospital Butterworth.

(S) FBG

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Congenital Inadequacy of the Cervix as a Cause of Infertility

(By S. W. Trythall, A.B., M.D., F.A.C.S., Detroit Michigan)

Factors responsible for successful termination of sterility cases studied in our office proved that patients falling in the relative infertility group had opened a channel of investigation leading to one of the specific causes of premature delivery in

the nullipara. This is the problem presented by the pathological lower uterine segment which we* feel is of congenital origin.

From this review, the women in the above categories revealed pathology amenable to corrective treatment as follows:

First, by preventive therapy in thirteen prima gravidas with congenital inadequacy of the cervix. Early recognition made it possible to deliver 11 viable babies, thus avoiding neonatal death and a subsequent relative infertility.

Second, by preventive therapy in ten of the nineteen multigravidas who by history have congenital inadequacy. In these women investigation revealed that of their multiple early deliveries, the first one terminated prematurely without traumatic incidence to the cervix.

Third, by the use of the Lash technique or its modification in the tracheoplasty operation in fifteen of the above women.

The author encountered his first problem of the inadequate cervix twenty-two years ago and subsequently has had moderate success by conization of the internal os as Steinberg(16) reported at the International Fertility Association meetings in Naples in 1956. This procedure has been replaced by a modification of the Lash tracheoplasty technique.

From a survey of the literature and discussion by fellow practitioners of the causes and treatment of premature delivery, one suspects a lack of understanding of cervical inadequacy as one of the multiple and complex causes of early termination of pregnancy.

In a study of the modern textbooks, it was noted that Greenhill,(6) Eastman,(3) and Titus(18) were the only authors writing in detail of this important facet of the problem of premature labor.

Therefore, those of us working in obstetrics and infertility should be grateful to Dr. Abraham Lash for bringing into focus the problems of a group of relatively infertile women in whom no endocrine or wheat-germ routine would prevent an early delivery.

The definitive diagnosis and surgical correction of the incompetent cervical os was first correlated by him from the world literature which included the investigations of J. J. Fisher(5) personal communications with N. Sproat Heaney as quoted by

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Presented at the June, 1957 meeting of the American Obstetrical Society in New York.

Dr. Lash (7) and the studies of Palmer (11, 18) and Lacomme (11). Lash was distressed by the paucity of literature available during the past twenty-five years on this subject of second trimester abortion due to the incompetent cervix. The material was summarized in his two important papers, i.e., Lash and Lash, 1950 (7) and Rubovits, Cooperman, and Lash, 1953 (15).

The senior Dr. Lash, reporting to the International Infertility Association in Naples in May, 1956 (6) discussed the results of 44 tracheoplastics for this type of habitual abortion. He was able to follow thirty-four of these patients, showing viable pregnancies after surgery in twenty-nine (85 per cent).

However, in the original work of Lash and that of the few other men who report this problem, the traumatic factors of previous pregnancy, abortion, and cervical trauma were given as the predominant causes. A characteristic statement was, "In virtually all of our cases there was an antecedent history of trauma to the cervix (15)."

In our study of patients with inadequate cervices, it was found that 32 per cent had had no previous pregnancy, abortion, or curettage. These cases without forewarning had lower uterine segments which became completely effaced and dilated early in the second trimester. We believe these are the women who have a congential inadequacy of the cervix. When not detected, they will continue to contribute to the high premature death rate because of repeated early termination of pregnancies resulting in relatively infertile marriages. In our work we became aware that by frequent vaginal examinations we were able to detect the early effacement of the cervix. This occurs over an extended period of time in preparation of the uterus for premature delivery. This is in agreement with the recent publication of work done on the "Prevention of Premature Delivery" as reported by Dr. L. J. Stephens. (17) The definitive diagnosis must be made early and the proper treatment instituted if the pregnancy is to be carried at least to viability.

The importance of this problem of premature delivery in our state is emphasized by the following facts as reported by Dr. G. Corneliuson of the Michigan Department of Health: "(a) Prematurity is still the greatest cause of death in children; and (b) Prematurity ranks 7th as a cause of all deaths." (2)

Majewski and Jennings bring us abreast of the times in stating that between 6 and 7 per cent of the total United States births have been consistently premature. (9)

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Great strides have been made in the past ten years in the reduction of neonatal death rates by the improved obstetrical care of the newborn. This has been accomplished largely by the work of Beck (1) and Potter (13, 14) in emphasizing the responsibility of the obstetrician for the first twenty-four hours of the infant's life.

By 1950, the year that terminated my ten-year study of perinatal morbidity and mortality at Crittenton General Hospital in Detroit, (19) it was possible to cut our rate by almost 50 per cent because of improved antenatal, intrapartum and postpartum care. At that time my attention was focused upon a discouragingly large group of the second trimester deaths of no known cause except prematurity.

Since then, the percentages in Michigan have remained almost static. In 1950, the neonatal death rate was 6.6 per 1,000. In 1955 it was 6.4. In 1955 there were 14,000 premature births or 7.3 per cent. This group accounted for 49 per cent of the fetal deaths.(2)

The author believes that early diagnosis of the inadequate lower uterine segment by all men practicing obstetrics would start a new trend which could change this figure to one which will begin to approach the irreducible minimum, as we are now experiencing in maternal mortality statistics.

The ideal method for the further reduction of the above figures as discussed by Potter(13) is a prophylaxis against the early delivery, thus circumventing the difficult task of caring for the immature infant.

In our office, one method used for preventing the premature delivery is the early diagnosis of the congenital inadequacy of the cervix. This has been facilitated by the fact that these women are infertility case studies and a complete investigation offered clues that they should be followed more closely than the routine pregnancies.

In the prima gravida group, it was noted that only one out of thirteen demonstrated abnormal hormone assays.

In the multigravida group, there were nineteen with relative infertility because of repeated premature terminations of pregnancy. Careful analysis of their histories including hospital records revealed no trauma to the lower uterine segment. When beginning treatment at our office, the women had a total of forty-seven conceptions with only a 20 per cent fetal salvage because of an apparent inadequate lower uterine segment. We,

therefore, consider them to be a badly neglected congenital type.

The following signs and symptoms were found in the majority of all cases:

1. The examination revealed a 5/6 to 1/6 corpus cervical ratio or a combination of hypogenital characteristics.

2. Ethiodal studies revealed that in a majority of the patients there is an abnormal uterine contour. The predominate variation presented is an arcuate type with a tendency to the bicornuate pattern. There is a consequent loss of the normal cervicocorpus angle which gives the cavity a truncated appearance.

Dr. Frederick Falls in a recent discussion of a paper on the cause of premature delivery stated that following a good many years of study of the configuration of the uterus he finds a rather large percentage of abnormality in habitual abortion problems. (4)

3. The Basal Body Temperature variations are minimal and nonconstant in the majority of these cases offering a clue to an approaching problem. No amount of hormones changed the temperature patterns. The patient took 450 milligrams of oral progesterone per day for 26 weeks.

4. Lower abdominal pressure, excessive painful uterine contractions, persistent dysuria, and rectal irritability were premonitory findings which could not be ignored if the diagnosis were to be made early.

5. Fetal movement becomes quiet from increased intra-uterine tension once effacement and dilatation occur.

Suspected patients are carefully instructed and asked to advise us when any one of the preceding conditions occurs. Speculum and vaginal examinations are mandatory in these women every five to seven days beginning in the second trimester. The definitive diagnosis is made on feeling and seeing complete effacement and at least 2 or 3 centimeters of cervical dilatation with the membrane presenting.

The inadequate cervix should be detected before the membrane is extruded through the os into a sphere because when this does occur, the total intra-uterine volume is diminished, the cervix contracts, and shearing of the placental bed may result in uterine bleeding before the rupture of the membranes.

This leads to a confusion in diagnosis of the true etiology causing the termination of pregnancy.

The membrane may present as a hemisphere as visualized in twenty of our cases of the inadequate cervix. With treatment relieving the hydrostatic pressure on the segment, the secundines will retract and the cervix close. Our experience has proved that this is a type of threatened abortion for which bed rest is one of the remedies.

Our first method of treatment then is that of preventive therapy in order to circumvent the early delivery:

1. Bed rest, high Trendelenburg, until the cervix closes
2. Bathroom and laxative privileges
3. Prophylaxis against intra-abdominal pressure
4. Carefully adjusted maternity corset
5. Lutrexin tablets, 4 STAT—three, two, one each hour until the contractions and uterine tension decrease in those patients with uterine irritability.
6. House calls
7. Termination of pregnancy by appointment to avoid a precipitous home delivery.

We have used Lutrexin since its introduction to the market.* Patients have been instructed when and how to use this medication and to tabulate its effectiveness. Of the women given this preparation, 55 per cent report their ability to control the uterine contractions and symptoms with this drug.

After the cervix has closed, the membrane retracted, and the patient has a viable baby, she is given liberty commensurate with the adequacy of the cervix.

Following the above routine in the thirteen nulliparous women who had eighteen pregnancies with congenital inadequacy of the lower uterine segments, eleven infants (60 per cent) were carried to viability and survived. In seven patients the membranes ruptured before the twenty-sixth week resulting in fetal deaths.

In the multigravida group who had had a previous fetal salvage of 20 per cent, early visual diagnosis was made in ten cases. Of these babies, 80 per cent survived on the above conservative treatment.

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*Hynson, Westcott & Dunning, Inc., Baltimore, Maryland. Patients using Lutrexin were on individual prescription basis.

We realize that when bed rest might be necessary for as long as six months it may be extremely difficult for our patients. Therefore, we recommend tracheoplasty following delivery in all who have had a positive diagnosis by visual and digital examination of cervical inadequacy during pregnancy and confirmed by ethiodol studies.

We also recommend surgery for the women in whom the abnormality exists, proven by history and the Lash x-ray technique.

During the weeks that this paper was being completed, a woman in the above group who had successfully carried her last of five pregnancies to viability on conservative therapy, presented us with a second effacing dilating cervix at twenty-two weeks. Bed rest was impossible and, following a discussion with Dr. W. J. Mulligan,[10] it was decided to take a more positive approach to prevent the premature rupture of the membrane. Following his technique, a polyethylene (animal tested) 1/16 inch tubing was used as a purse string suture to close the cervix.

The writer believes that this definitive approach used in the early months of gestation in the women have bad histories of habitual abortion of this type would result in greater fetal salvage.

When indication for operation is not well defined, we prefer to observe the patient through a pregnancy before surgery.

We have used tracheoplasty in fifteen women. Six of these have not attempted to conceive. Seven have become pregnant and all have carried to term except one. This patient had a poor result from surgery and delivered a 3½ pound premature viable baby. Two who have conceived are in the third trimester with no forseeable difficulty.

The purpose of this paper is to emphasize three important factors:

1. The possible fetal salvage by the early recognition of the congenital inadequate lower uterine segment as a definite entity causing prematurity and relative infertility.
2. To further stimulate all doctors practicing obstetrics to use the simple inexpensive diagnostic device of more vaginal examinations in the second trimester.
3. To prove there is a positive approach to avoiding infertility and fetal wastage by a direct attack upon the consistent 7 per cent premature birth rate which resulted in 1200 neonatal deaths in Michigan in 1955.[2]

ACKNOWLEDGMENT

Gratitude is expressed to Drs. R. C. Jeremias and J. L. Gillard, my partners, who have spent many hours examining the patients cited in order to establish that congenital inadequacy of the cervix is a definite clinical entity as a cause for prematurity and relative infertility.

REFERENCES

1. Beck, A. C.: Obstetricians' responsibility for the first few days of life. Am. J. Obst. & Gynec., 51:173–183 (Feb.) 1946.
2. Corneliuson, Goldie: Personal correspondence, Michigan Department of Health, April, 1957.
3. Eastman, N. J.: Williams' Obstetrics. 11th Edition. New York: Appleton, Century, Cross, 1956.
4. Falls, Frederick: Discussion on uterine contractility, circulation, and urinary steroids in premature delivery. Am. J. Obst. & Gynec, 73:587 (Mar.) 1957.
5. Fisher, J. J.: The effect of amputation of the cervix uteri upon subsequent parturition. Am. J. Obst. & Gynec., 62:644, 1951.
6. Greenhill, J. P.: Obstetrics. 11th edition. Philadelphia: W. B. Saunders Co., 1955.
7. Lash, A. F., and Lash, S. R.: Habitual abortion: The incompetent internal os of the cervix. Am. J. Obst. & Gynec., 59:68–74 (Jan.) 1950.
8. Lash, A. F.: Paper delivered at International Infertil. Assn., Naples, Italy, May, 1956 and personal correspondence.
9. Majewski, J. T., and Jennings, T.: A uterine relaxing factor for premature labor. Obst. & Gynec., 5:649–652 (May) 1955.
10. Mulligan, W. J., Personal correspondence.
11. Palmer, R., and Lacomme, M.: La beance de Forifice interne, cause d'avortements a repetition? Une observation de dechirure cervicoisthmique reparee chirurgicalement, avec gestation a terme consecutive. Gynec. et Obst., 47:905 (Nov. 6) 1948.
12. Palmer, R.: role de la beance de l'isthme uterin dans l'avortement habituel. Rev. franc. gynec. et obst., 45:218 (Sept.-Oct.) 1950.
13. Potter, E.: The effects of infant mortality of vitamin K administered during labor. Am. J. Obst. & Gynec., 50:235–47 (Sept.) 1945.
14. Potter, E.: Pathology of the Fetus and Newborn, Chicago: Year Book Publishers, 1952.
15. Rubovits, F. E., Cooperman, N. R., and Lash, A. F.: Habitual abortion: A radiographic technique to demonstrate the incompetent internal os of the cervix. Am. J. Obst. & Gynec., 66:269–80 (Aug.) 1953.
16. Steinberg, W.: Treatment of cervical factor in sterility. Internat. J. Fertil., 2:71 (Jan.-Mar.) 1957.
17. Stephens, L. J.: Correspondence, prevention of premature delivery. Am. J. Obst. & Gynec., 76:694–695 (Mar.) 1957.
18. Willson, Titus: Management of Obstetric Difficulties, 5th edition. St. Louis: C. V. Mosby Co., 1955.
19. Trythall, S. W.: Possible infant salvage at Florence Crittenton Hospital. J. Michigan State M. Soc., 46:1385–1388 (Dec.) 1947.

Congenital Inadequacy of the Lower Uterine Segment as One Cause of Habitual Abortion

(Sylvester W. Trythall, M.D., F.A.C.S., and Robert C. Jeremias, M.D.)

The Purpose

IN our city this past year Drs. A. Lash (1) and R. Barter, (2) two of the foremost exponents of the incompetent cervix in our country, have discussed the inadequate cervix. Unequivocally they state that in their work congenital factors played a small role.

This paper is presented in order to report first, that in our office the inadequate lower uterine segment of congenital etiology is one of the most important causes of premature delivery, second to alert all those responsible for the care of pregnant women that the simple inexpensive diagnostic device of the weekly or bi-weekly vaginal examination after the twelfth week was our most important of all diagnostic devices. We are convinced that this routine has materially reduced our static 6 to 7(3) per cent premature birth rate and decreased our percentage of prematurity of no known cause.

In Michigan in 1956, (4) there were 14,000 premature births accounting for 49 percent of fetal deaths.

Eastman (5) in discussing, "The problems of the Evolution of Obstetrics", agrees that one half of neo-natal deaths are caused by prematurity as well as one-third of all problems of cerebral palsy. He states that in 60 per cent of these early deliveries the cause is unknown. He states that these births represent in essence some defect in one of the basic phenomena of reproduction, that of uterine contractility. Our experience with the majority of our congenitally inadequate uteri substantiate the idea that uterine irritability (6) is the most important part of a complex syndrome which must be identified early by the patient and the doctor if a threatened premature delivery is to be avoided.

Dr. Stallworthy (7) stressed at the I.F.A. Amsterdam meeting the practical fact that if we considered each pregnancy as a possible habitual abortion, more careful analysis for all the probable causal factors would result in fewer women being classed as chronic aborters.

We could find no standard definition in the literature, but from our work we propose that the primigravida be classified as having the "Congenital Inadequate Lower Uterine Segment" when digital and visual examination in the second trimester reveals effacement and 1 to 2 centimeters dilation of the cervix from painless uterine contractions. The patient must have had no previous cervical trauma more significant than an endometrial biopsy by a specialist. We recognize that this is an unsatisfactory method lacking controls, and it is the work of men like Bonilla (8) and Mann that will make a direct approach possible.

Dr. Mann's (9) group reporting on the "Sphincteric Function of the Uterine Isthmus" at the American Roentgen Society Meeting said that to date, 350 habitual aborters, 100 nonaborting controls have been studied. The X-ray findings coupled with clinical follow-up revealed that cervical incompetence can now be diagnosed in the nonpregnant state and that the sphincteric disability resides in the isthmus rather than the cervix.

The Material

The case histories on which this investigation is based are provided by the past 3000 women of our private obstetrical and infertility practice. These are divided into 3 groups:

(a) The 27 primigravida patients who have demonstrated congenital inadequacy as has been defined.

(b) The 27 multigravida women under our care who by history, examination, and careful observation of a pregnancy have also indicated incompetency. In these women, complete investigation of the records revealed that the first of their multiple early deliveries terminated in the second trimester without pain or forewarning. These patients lead us to suspect they have been a badly neglected congenitally inadequate group.

(c) The 25 women who have had traumatic cervical incidents—this group is not included in this discussion.

Methods Used in the Diagnosis

(a) Careful, detailed evaluation of the genital tract with special attention to hypogenital characteristics: the cervix is measured with the uterine sound, and the internal os is cali-

brated with Hegar dilators. The short cervix was the most constant finding.

(b) Definite ethiodol studies in suspected cases, with standardized technique employed by the same operator. 84 per cent of the patients in today's report had Salpingograms. Dr. Kamm (10) reporting at the I. F .A. Amsterdam meeting stressed the need and importance of early X-ray study in abortion. Our ethiodol studies in these first two groups of women demonstrated four major intra-uterine contours:

(1) The majority were those with the predominant defect of an arcurate, long-truncated funnel type.

(2) The second in importance was the tricuspid.

(3) The third showed abnormally small cavities.

(4) Those with normal uterine contours were in the minority.

(c) Weekly or bi-weekly vaginal examination in all questionable and older primigravida after the twelfth week was the most definitive, and important diagnostic device. Our combined 40 years experience has taught us that pregnancy itself is the only reliable test for uterine adequacy.

(d) We alert the suspected patients to report to the office if they have an increased uterine irritability as indicated by:

1. An awareness of consistent rhythmical painless contractions.
2. Increasing dysuria.
3. Increasing rectal pressure or irritability.
4. Pulling sensation in the groin.
5. A feeling that suddenly the baby is very low and a sense of fullness in the pelvis.

Treatment

Conservative therapy is the most important and is used for all these irritable uteri until they are stabilized and the cervix closes. Experience has shown that it is poor technique to place a purse-string suture in the uterus which is already irritable.

We have learned that conservative therapy throughout the first pregnancy is best in:

(a) The patients of unknown uterine capacity.

(b) The women who by X-ray have demonstrated small uterine cavities.

We have discontinued tracheoplasty in this latter group.

CONSERVATIVE THERAPY CONSISTS OF:

1. Bed rest in high Trendelenberg.
2. Bathroom and laxative privileges.
3. Carefully adjusted maternity garment.
4. Prophylaxis against intra-abdominal pressure.
5. Sufficient sedation to maintain patient at rest.
6. *Lutrexin 4 stat repeat q 4 hrs. & p. r. n. until uterine contractions are controlled.

We have used the non-steroid extract of the pregnant sow's ovary, and 80 per cent of our patients with congenital lower uterine segment problems report their ability to control excessive uterine contractility and associated symptoms with this preparation. Our careful observation leads us to believe that this material has a quieting effect on the irritable uterine muscle. Massive doses have been (8) required in a few patients with no deleterious effects.

I would like to stress that we have not used surgery without a clinically proven inadequacy as required by our definition.

We have, however, altered our approach in the problems of the inadequate lower uterine segment. We reported surgery Palmer (11)-Lash (12) type as the treatment of choice for all proven inadequacy at the A. S. S. meeting in 1957. (13) Now in 1959 definitive therapy, consisting of either conservative treatment or the polyethylene circlage suture, is used during pregnancy as the individual case demands.

The women who by ethiodol study have long-truncated cavities are operated on by Dr. Jeremias in the second pregnancy when frequent examination reveals effacement and dilatation in the second trimester. He uses one or two .067" animal-tested polyethylene sutures which are placed to simulate the normal two-thirds to one-third ratio of the uterine contour. To date we have placed 18 such sutures. All of our nonabsorbent sutures are permanent but are available for cutting and removal if necessary. At present we have 5 pregnancies doing well following this therapy. One patient has had nine previous deliveries with non-viable infants. She is now at term.

From our experiences with 24 tracheoplasty operations in these two groups, we have decided to reserve this procedure for the traumatic cervix before a subsequent pregnancy. Because of poor healing we have encountered, the repair is now

*Hynson, Westcott & Dunning, Inc., Baltimore, Maryland

reinformed by one or two permanent but removable .067" polyethylene Mulligan (15)-Shirodkar (16) type sutures which are placed just beneath the vaginal mucosa and are carried out and tied high in the posterior fornix.

Our Results

In the congenital group, 27 patients have had 55 pregnancies; 33 babies survived. *Conservative therapy* was responsible for success in 77.4 per cent. Tracheoplasty contributed 9.7 per cent. Polyethylene circlage, 12.9 per cent.

Before treatment in the second or suspected congenital patients, 27 women had 73 pregnancies; 10 infants or 13.7 per cent survived.

During the interval these patients have been under our care, they have had an additional 32 conceptions. 23 babies or 71.9 per cent were viable following therapy which involved 52 per cent conservative treatment and 48 per cent surgical. The surgery involved 22 per cent polyethylene sutures and 26 per cent modified Palmer-Lash trachelorrhaphy.

Summary

1. We have endeavored to establish by direct or indirect methods a classification which would differentiate the cases of congenital uterine inadequacy from those of traumatic origin, both of which are responsible for premature delivery. The use of this classification in our practice has more definitely selected the patients to be subjected to surgery.

2. By employing our removable polyethylene purse-string suture, we are not committed to terminate the pregnancy by hysterotomy as are those using other synthetic mesh material as reported by Barter (16).

3. We feel that by urging all practitioners to employ the simple, inexpensive diagnostic device of frequent vaginal examination during the second trimester, the syndrome of uterine irritability and of the inadequate cervix will be recognized early enough to institute definitive therapy and thus cut down on the consistent 7 per cent (17) premature delivery rate in our country.

4. Our experience with medical treatment of the uterus with excessive irritability and congenital inadequacy would indicate that all practitioners without available hospital and surgical

privileges could expect reasonable success on conservative therapy.

REFERENCES

1. Lash, A. F. Michigan Soc. of Obst. & Gynec. Meeting with Grace Hospital, Detroit, Dec. 2, 1958.
2. Barter, R. First Annual Obst. & Gynec. Residents Day—Wayne State U. Feb. 23, 1959.
3. Majewski, J. T., and Jennings, T. *Obst. & Gynec.* 5:649, 1955.
4. Corneliuson, G. Mich. Dept. of Health, April 1957.
5. Eastman, N. J., *J.A.M.A.* 117:1293, 1959.
6. Falls, F. *Am. J. Obst. & Gynec.* 75:587, March 1957.
7. Stallworthy, J. *Internat. J. Fertil.* Sept. 1959, Vol. 4, No. 3. P. 241.
8. Bonilla, F., Spain B. S. D. 31: Cervical incompetence of congenital origin. Third World Congress on Fertility and Sterility, Amsterdam, Holland.
9. Mann, E. C., M.D.—David Hyat, M.D. Personal Communications. Nov. 3, 1959.
10. Kamm, M. L. B.S.D. 32: Congenital uterine abnormalities in habitual abortion and premature labor. Third World Congress on Fertility & Sterility, Amsterdam, Holland.
11. Palmer, F., and Lacomme, M. *Gynec. & Obst.* 47:905, 1948.
12. Lash, A. F., and Lash, S. R. Chicago Gynec. Society. Oct. 15, 1948.
13. Trythall, S. W. *Mich. State Med. Journal* Vol. 57:711–714, May, 1958.
14. Mulligan, W. J. Personal Communications, April, 1958.
15. Shirodkar, V. N. *Antiseptic* 52:299, 1955.
16. Barter, R. H. *Surgical Forum* 1957, Vol. 2.
17. Stephens, L. J. Correspondence. Prevention of premature delivery. *Am. J. Obst. & Gynec.* 73–694–695, March, 1957.

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The Action of Aqueous Corpus Luteum Extract Upon Uterine Activity

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The activity of aqueous extracts of corpus luteum on the uterus has been the subject of many investigations. Most of these investigations have involved the use of excised muscle or physiologically altered animals. Either ovariectomy or exposure of the uterus through the abdominal wall in such a manner as to permit insertion of a balloon, or sections of the uterus placed in a water bath are typical of these alterations. The

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physiological picture in either of the foregoing methods does not simulate the normal physiological picture as does the method herein described. The excised muscle test proved to be entirely nonspecific when used by us in the early part of this investigation. Twenty-six substances were tested and the excised uterus from pregnant mice was used in the water bath. Among the substances studied were those found in the aqueous corpus luteum preparation, or materials which were used in the manufacturing process of aqueous corpus luteum. Other unrelated compounds were tested in order to gain a broad view of the specificity of the reaction of the uterine section in the water bath.

The observation of Riley that chloretone relaxes the excised uterus was confirmed, but 15 of the 26 other substances studied by us also caused similar relaxation. Acids of the acetic and butyric type gave marked relaxation although sulfuric acid showed no effect. Boric acid caused a tension. The variation of *p*H caused a change in uterine effect. Atropine sulfate 0.5 per cent caused tension, while procaine hydrochloride 1 per cent produced no effect. Progesterone saturated aqueous solution caused a diminution of activity but no marked relaxation. Tricresol and tween 80 were among those substances eliciting relaxation of the muscle. The aqueous corpus luteum preparations studied gave a wide variation of effects from complete relaxation to marked tension of the muscle by simply manipulating the *p*H of the solutions.

Recently Riley showed that commercial samples of corpus luteum were capable of reducing the activity of the rabbit's uterus in vitro and in vivo. He demonstrated further that the relaxant action was presumably due to the 0.25 to 0.5 per cent of chlorobutanol present in the extracts as a preservative. Some aqueous corpus luteum preparations which were devoid of the preservative were reported by this investigator to be without relaxant action on the uterus. In addition, as mentioned above, Riley showed that solutions of chlorobutanol of the foregoing concentrations were capable of producing diminution of the activity of isolated uterine strip. In the light of these observations, it was suggested that the activity of aqueous extracts of corpus luteum owe their relaxant action to the presence of chlorobutanol "rather than to some heretofore unrecognized property of the corpus luteum."

As it was found that the excised section test was so unreliable, in the present investigation animal tests with the uterus intact were used. After many experiments on mice, rats, rabbits, and guinea pigs, an in vivo method has been designed whereby the relaxant action of aqueous corpus luteum can be positively demonstrated on the uterus *in situ*. This phenomenon of relaxation was observed during a series of experiments with guinea pigs, while investigation was made of the suggested reversal of adrenalin activity by the aqueous corpus luteum preparations (3). A definite relaxation of tonus and decrease in amplitude of contractions of the uterus were apparent after a single intravenous injection of aqueous corpus luteum. In many cases it was found that the activity of the uterus ceased completely for several minutes.

The present method of assay is based on the creation and maintenance in the test animal of a uniform endocrine picture. It is, unfortunately, not practical to use naturally pregnant animals because of uncertainty as to the stage of pregnancy. As a consequence, it was necessary to produce artificialy a uniform state of uterine activity in the test animal by the use of estrogenic injections. The injection of 0.1 milligram of diovocylin per animal subcutaneously 7 to 12 days before use caused proliferation of the uterus, in size, equal to approximately that of a 20 day pregnancy. The guinea pig's uterus so prepared exhibited in most cases a regular pattern of activity when attached to the kymograph (Fig. I), as described here.

The test animals used were young virgin guinea pigs, weighing about 250 to 300 grams at the time the primer injection of estrone was given, and in no instance were castrates used. They gain weight during the 7 to 12 day period before the test and usually weigh about 350 grams at the time of the test. Guinea pigs at this weight are approaching sexual maturity. A number of pigs failed to demonstrate a normal uterine activity, and this lack of such activity was much more evident in the animals weighing 400 grams or over at the time of the test. Any animal failing to give a regular pattern of uterine activity for a 10 to 15 minute control period was discarded. It is important that the temperature of the saline spray remain fairly constant because temperature variation definitely affects the uterine activity. Young female rabbits were also used in this test method and also responded to the aqueous corpus luteum.

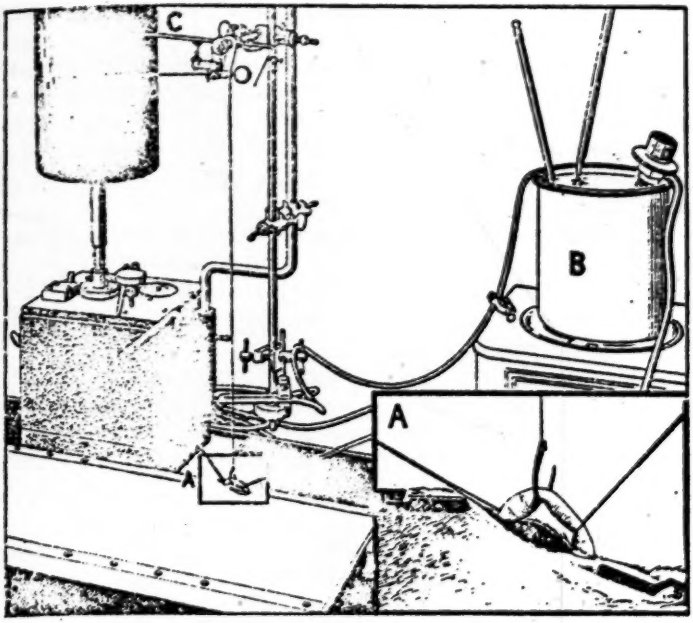


Fig. I. Drawing showing apparatus and technique of making tracings of activity of uterus. The animal is placed on the table at lower left of drawing, and as shown in inset A, the uterus is exteriorized and the muscle is attached to the writing lever.

The primed guinea pig is anesthetized by the injection intraperitoneally of 50 per cent urethane, approximately 1 cubic centimeter per animal. The uterus is exteriorized through a midline abdominal incision, and the muscle is attached to the writing lever as shown in Figure 1. A length of the uterus on either side of the half-curved needle, used to attach the uterus, was supported by loosely fitting cords so as to lift the muscle free of the other abdominal movements. Throughout the experiment the uterus was kept moist and maintained at body temperature by a warm saline solution spray. The jugular vein was exposed for purpose of injections, and all test injections were made intravenously throughout these experiments. The constancy and reliability of this method have been proved by the number of tests (61) done in this series.

SUBSTANCES STUDIED*

1. The first substance injected was a commercial aqueous lutein solution 2 cubic centimeters per kilogram, containing no chlorobutanol. Forty injections were made into 17 guinea pigs. Invariably a diminution in uterine activity was experienced. A typical tracing is shown in Figure 2. The rabbit's uterus responded in a similar manner (2 animals).

2. Solutions of chlorobutanol were injected (2 c.c. per kgm. of a 0.25 per cent solution). Twelve injections were made into 4 pigs. No diminution of the activity of the uterus was elicited by the substance upon intravenous injection. A typical tracing is shown in Figure 3.

3. Commercial aqueous extracts of corpus luteum identical with No. 1, containing 0.25 per cent of chlorobutanol, were injected. Nine injections were made into 3 guinea pigs. In no instance did the presence of chlorobutanol enhance the activity of corpus luteum extract upon the uterus. A comparison is shown in Figure 4.

One uterine horn of the animal represented by Figure 3 was extirpated and studied as a smooth muscle preparation in vitro. Figure 5 shows it was relaxed by chlorobutanol similar to results obtained by Riley.

It becomes clear upon examination of the tracing in Figures 2, 3, 4, and 5 that aqueous corpus luteum extract contains an active principle which, when carried to the uterus via the circulation, causes a diminution in uterine activity and tonus. The work of Hisaw and his associates (1, 2) at Harvard is confirmed in the observed uterine relaxant activity. It is also evident that this systemic action is not dependent upon the presence of the preservative chlorobutanol as the older methods of testing might suggest. Furthermore it appears that chlorobutanol is incapable of enhancing the uterine relaxant action of corpus luteum extract, as shown by this technique.

In order to determine whether or not this characteristic uterine relaxant activity manifested by the corpus luteum extracts could be produced by progesterone, the following experiments were performed:

Progesterone (5 mgm. per c.c.) was dissolved in tween 80.5 per cent, and injected intravenously, following our described technique. No relaxing effect upon the uterus *in situ* was pro-

*Figures 2, 3, 4 and 5 omitted.

duced. Progesterone in aqueous suspension 5 milligrams per cubic centimeter was also used and found to elicit no effect.

In order to determine whether or not the action of the corpus luteum preparation was specific or due to some nonspecific constituent extractable by the manufacturing process, a control experiment was carried out. Since the commercial corpus luteum preparation used in these experiments was an extract of the sow's ovaries, a portion of the fresh intestine of the sow was subjected to the exact process used in preparing the commercial corpus luteum. This intestinal extract was tested on the guinea pig's uterus and found to elicit no relaxant activity.

CONCLUSIONS

1. Extracts of corpus luteum have been shown to produce relaxation of the uterus of the guinea pig and rabbit (previously primed with estrone) *in situ*, upon intravenous injection.
2. This action is not due to the presence of the preservative chlorobutanol.
3. A laboratory method has been perfected for demonstrating the relaxant activity of aqueous corpus luteum in the living animal.

REFERENCES

1. ABRAMOWITZ, A. A., MONEY, W. L., ZARROW, M. X., TALMAGE, R. V. N., KLEINHOLZ, L. H., and HISAW, F. L. Endocrinology, 1944, 34 : 103.
2. ALBERT A., MONEY, W. L., and ZARROW, M. X. Endocrinology, 1946, 39 : 270.
3. BEST, H., and TAYLOR, N. B. Physiological Basis of Medical Practice, 3d ed., p. 1264 (c). Baltimore : Williams & Wilkins Co., 1943.
4. MILLER, NORMAN F., PARROTT, MAX H., STRYKER, JOAN, RILEY, G. M., and CURTIS, ARTHUR H. Leucoplakia of the vulva. Am. J. Obst., 1947, 54 : 40.

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The Effects of Ovarian Extracts Upon Activity of the Guinea Pig Uterus in Situ

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The presence of a substance in aqueous extracts of sow corpora lutea which possesses the ability to diminish the tone and abolish spontaneous contractions of the guinea pig uterus *in situ* was demonstrated by Krantz, Bryant and Carr (1950).

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Tests of a total of 26 samples of biological material and pharmacologically active substances, including epinephrine, acetylcholine, tyramine, chlorobutanol, and cobra venom, indicate that the response is highly specific for luteal extracts. The object of the present paper is to describe some of the chemical properties of the active substance (which we have termed 'uterine relaxing factor' (URF)), and to compare its properties and distribution with known ovarian hormones.

Experimental.—The bioassay of URF requires a test animal with a uniform, reproducible state of uterine activity. Uteri of pregnant guinea pigs, while suitable in some respects, were unreliable because of uncertainty as to the stage of pregnancy. A uniform motility may be produced by the administration of estrogen, and, in the experiments reported here, 0.10 mgm. *a*-estradiol propionate (Ciba) was injected daily into guinea pigs for seven to twelve days prior to the assay. This treatment causes growth of the uterus approximately comparable to that observed on the twentieth day of normal pregnancy. The animals found to be most satisfactory were young virgin females, weighing 300–350 gm. at the first priming injection. When used for assay 7–12 days later the animals were of early sexual maturity and weighed 350–400 gm. Such animals exhibit a regular pattern of activity when the uterus is exposed under urethane anesthesia. Animals failing to display regular patterns for a control period of 10–15 min. were discarded. The method of exposing the uterus and recording motility has been described elsewhere (Krantz, Bryant and Carr, 1950).

The unit of URF activity was arbitrarily established as the minimal amount which, when injected intravenously into the estrogen-treated guinea pig, effects a 90 per cent reduction in the height of spontaneous contractions for a period of at least ten minutes. Each sample tested was assayed at a minimum of three levels, the ratios of which were usually 1.0:0.75:0.56; the actual amounts selected were such that the three levels tested bridged the unit response as defined above. Three animals were used for each dose level. Estimates of relative URF content, therefore, are considered to be reliable to within ±50 per cent.

Most of the URF preparations used in this study were made by dilute HCl extraction of dried, methanol extracted, unselected sows' ovaries. The filtered extract was brought to pH

6.5 and inactive material removed by filtration. The active fraction is contained in the precipitate, contaminated with relatively large quantities of ammonium sulfate and inactive protein. The former is removed by dialysis.

Relaxin was prepared from the ovaries of pregnant sows by the method of Frieden and Hisaw (1950). Pregnant rabbit serum was concentrated by the method of Albert and Money (1946). Relaxin assays were performed on groups of eight to ten guinea pigs according to the technique described previously (Frieden and Hisaw, 1950). Each preparation was assayed at three or more serial dilutions, chosen to correspond to the injection of from 0.5 2.0 guinea pig units (GPU). The reliability of estimates of relaxin content thus approximates that of most serial dilution assays (±100 per cent).

Results. Chemical properties of URF.—The substance in ovarian extracts which is responsible for uterine relaxation appears to be very stable. Exposure of URF solutions to 100°C. for five minutes results in but slight diminution of activity; solutions kept at 40°C. for two years likewise showed negligible losses. Most of the activity is retained following twelve-hour dialysis against running tap water.

The effects of reducing agents and proteolytic enzymes are indicated in table 1. Both trypsin and pepsin readily inactivate URF, as do cysteine, glutathione, sodium thioglycollate, BAL, ascorbic acid, and sodium bisulfite.

TABLE 1.—*Effects of reducing agents and enzymes upon URF preparations*

Reagent	Concentration (mgm./ml.)	pH	Reaction time (hr.)	Percent inactivation
Cysteine	1	5.9	1	100
Glutathione	21	7.4	1	75
Sodium thioglycollate	8	7.7	20	100
Ascorbic acid	13	7.6	20	95
BAL (dimercaptopropanol)	8	7.7	20	75
Sodium bisulfite	5	6.8	10	50
Trypsin	2	7.7	24 at 37°C.	100
Pepsin	2	1.5	24 at 37°C.	100

Final concentration of URF = 1.0 mgm./ml.
Unless otherwise indicated, mixtures were allowed to react at room temperature (25°C).

URF and relaxin.—It seems clear, from a consideration of the method of preparation and the properties of active extracts, that the phenomenon of uterine relaxation is not referable to the action of an ovarian steroid. Explicit elimination of the possibility that contamination with progesterone was responsible for the observed effect was afforded by experiments in which the injection of as much as 50 mgm. of this compound was shown to be without effect. On the other hand, the properties described above suggest that the active agent is probably protein- or peptide-like in nature. Since the only other non-steroidal physiologically active agent which has so far been isolated from ovarian tissues, namely relaxin, also appears to be a protein (Frieden, 1951a), it was of obvious interest to compare the properties of URF with those of relaxin. The chemical properties of URF parallel, with considerable fidelity, those of relaxin. Like the former, the latter is a heat-stable, slowly dialyzable substance, sensitive to proteolytic enzymes and a variety of reducing agents (Frieden, 1951a, b).[2]

Assays of URF activity were performed on a total of eight relaxin preparations, ranging in specific activity from 5 to 450 GPU per milligram. It may be seen (table 2) that all of these preparations possess the ability to diminish the motility of the uterus under the conditions of the URF assay. It further may be noted that preparations of high relaxin content (52–15, 66–4, 78–19) were found to be the most active with respect to URF content. However, the ratios of the two activities varied from 1:1 (preparations 79–1) to 1:8 (preparation 50–1).

Six URF preparations were tested for relaxin content (table 3); in but one instance was the ratio of relaxin to URF activity as high as 1:2, and in most instances the ratio was considerably smaller. Together, the data of tables 2 and 3 indicate that the ratio of relaxin to URF activity may vary over a twenty-fold range. While uncertainties in both assay methods may contribute to this variation, the wide divergence of relative potencies cannot be explained entirely on this basis.

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[2] Ascorbic acid appears to cause rather more inactivation of URF than of relaxin, while the opposite seems to be true for the action of sodium bisulfite. Differences in reaction time, reagent concentration or pH may account for these discrepancies.

TABLE 2.—*Comparative assays of relaxin preparations*

Preparation No.	Relaxin content (GPU/mgm.)	URF content (units/mgm.)
46-1	15	35
50-1	5	40
52-14	150	250
52-15	100	200
52-16	25	150
66-4	450	1, 000
77-19	300	500
79-1	70	70

TABLE 3.—*Comparative assays of URF preparations*

Preparation No.	Relaxin content (GPU/mgm.)	URF content (units/mgm.)
W.O. 31	1. 0	3
R-70-1	3. 0	6
R-11	. 5	8
R-86-2	5. 0	36
R-6A	<5. 0	100
1212	20 (per ml.)	200 (per ml.)

Studies of the comparative electrophoretic behavior of URF and relaxin serve further to emphasize the similarity between the two substances. Although neither has been obtained in electrophoretically homogeneous form, assays of the various cell fractions following electrophoresis of URF and relaxin preparations indicate that both are anionic at pH 7.7 and cationic at pH 6.0., i.e., both isoelectric points lie between these limits. The assay data also indicate that, at both pHs, the relative rates of migration of the two substances are, within limits of assay error, the same.

The relaxin content of the sow ovary has been shown to increase markedly during pregnancy. Thus, while the ovary of the mature, non-pregnant sow contains less than 25 GPU of relaxin per gram, those collected late in pregnancy contain from 300–1000 GPU/gm. (Frieden and Hisaw, 1950). It has also been demonstrated that relaxin is present in high concentration

in the serum of pregnant rabbits after the 24th day of pregnancy, while none can be detected in the blood of non-pregnant females [3] or males (Abramowitz *et al.*, 1944). To define further the relationship between URF and relaxin, extracts of selected lots of sows' ovaries and of pregnant rabbit serum and of male rabbit serum were assayed for URF activity.

The results of these experiments indicated that there exists a significant correlation between the tissue distribution of URF and that of relaxin. Extracts of ovaries of immature sows contain barely detectable quantities of URF. Larger amounts may be found in ovaries from mature animals, containing functional corpora lutea,[4] while the most active extracts are obtained from ovaries of animals in which pregnancy is well advanced. Like relaxin, URF is found in the blood of pregnant rabbits, while the blood of male rabbits is inactive. The serum of pregnant women also contains URF, as does the urine of pregnant women and pregnant cows.

Discussion.—It is not yet possible, on the basis of the data so far obtained, to define precisely the relationship between URF and relaxin. While the persistence of URF activity in purified relaxin preparations may be no more than coincidental, our data best fit the hypothesis that at least two substances will induce uterine relaxation and that relaxin is one of these. The chemical similarity between the two substances, as well as the observation that relaxin-poor URF is also found in the ovary, and apparently particularly concentrated in those with functional corpora lutea, suggests that we are dealing with two related compounds, with relaxin activity being confined to one of them.

Relaxin, or a substance with similar physiological activity, is found in the blood of a number of species of animals during pregnancy. (Hisaw and Zarrow, 1950), although only in guinea pigs has its presence been correlated definitely with relaxation of the symphysis pubis. The physiological significance of relaxin in such species is, as yet, without satisfactory explanation. The observations reported here suggest the possibility that relaxin may be concerned in the changes in myometrial activity

[3] Very small amounts of relaxin may appear in the blood of non-pregnant rabbits during pseudopregnancy.

[4] Some of these may have been in the very early stages of pregnancy.

associated with functional corpora lutea and pregnancy (see Reynolds, 1949). In early work on this problem, the suggestion was advanced (Robson and Illingworth, 1931; de Fremery, Luchs and Tausk, 1931, 1932) that the luteal factor responsible for inhibition of spontaneous myometrial activity was distinct from that responsible for progestational modification of the endometrium; this view fell into disfavor when it was later established that crystalline progesterone was capable of producing both effects (Allen and Reynolds, 1935; Robson, 1936). In view of the fact that progesterone is capable of inducing the formation of relaxin in tissues of the female reproductive tract (Hisaw and Zarrow, 1938; Zarrow, 1948), the possibility exists that the effects of progesterone are indirect, and mediated through relaxin.

SUMMARY

Studies of the chemical properties of a uterine relaxing factor (URF), obtained from aqueous extracts of sows' ovaries indicate that the active agent is non-dialyzable, stable to heat, and sensitive to the action of proteolytic enzymes and a variety of reducing agents. It is concluded that URF is a protein or polypeptide. URF activity is also displayed by both crude and purified relaxin preparations, and comparison of the occurrence of URF and relaxin in various tissues suggests a close relationship between the two substances.

The possible relationship of protein-like hormones of the reproductive tract to changes in uterine motility have been discussed.

REFERENCES

ABRAMOWITZ, A. A., MONEY, W. L., ZARROW, M. X., TALMAGE, R. V. N., KLEINHOLZ, L. H., AND HISAW, F. L.: Endocrinology, 34: 103, 1944.

ALBERT, A., AND MONEY, W. L.: Endocrinology, 38: 56, 1946.

ALLEN, W. M., *and* REYNOLDS, S. R. M.: Science, 82: 155, 1935.

DE FREMERY, P., LUCHS, A., AND TAUSK, M.: Nederl. Tijdsc. v. Geneesk., 75: 1669, 1931.

DE FREMERY, P., LUCHS, A., AND TAUSK, M.: Pfluger's Arch., 231: 341, 1932.

FRIEDEN, E. H.: Arch. Biochem., 30: 138, 1951a.

FRIEDEN, E. H.: Fed. Proc., 10: 184, 1951b.

FRIEDEN, E. H., AND HISAW, F. L.: Arch. Biochem., 29: 166, 1950.

HISAW, F. L., AND ZARROW, M. X.: Proc. Soc. Exper. Biol. Med., 69: 395, 1948.

HISAW, F. L., AND ZARROW, M. X.: in *Vitamins and Hormones*, Vol. 8., Academic Press, N. Y., 170, 1950.

KRANTZ, J. C., BRYANT, H. H., AND CARR, C. J.: Surg., Gyn. and Obstet., 90: 372, 1950.
REYNOLDS, S. R. M.: *Physiology of the Uterus*, 2nd. Ed., Paul B. Hoeber, N. Y., 87, 1949.
ROBISON, J. M.: J. Physiol., 88: 100, 1936.
ROBSON, J. M., AND ILLINGWORTH, R. E.: Quart. J. Exper. Physiol., 21: 93, 1931.
ZARROW, M. S.: Endocrinology, 42: 129, 1948.

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Treatment of the Dysmenorrhea Symptom Complex. A Preliminary Report on the Efficacy of a Uterine "Relaxing Factor"

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Dysmenorrhea is a symptom complex composed not only of menstrual cramps but generalized symptoms, backache, leg ache, headache, diarrhea, nausea and vomiting, and general malaise. There is a great difference of opinion as to the exact etiology of the syndrome. Most observers believe that both smooth-muscle contractions and vascular constriction are components. These are somehow related to the ovarian steroid pattern, as anovulatory menses are usually painless. Ancillary factors are also of prime importance, especially psychosomatic factors. These may be manifested as relatively mild tension states due to temporary work or living habits or may be much more serious immaturity problems. It is well recognized that it is important to control symptoms of dysmenorrhea as soon after the onset of the syndrome as possible, for it tends to become a habit pattern. The woman who has dysmenorrhea learns to look forward to her menses with dread which in itself, by creating additional tension, aggravates the condition.

There are many types of therapy available. Current concepts have been nicely summarized by Miller and Behrman.(1) Simple bed rest and heat applied to the lower abdomen have always been at times effective, but for the working adult these are frequently impractical. Analgesic drugs are acceptable

therapy. However, drugs which are habit forming should certainly be avoided and all too frequently we find that only these are effective. Antispasmodics are also used and have their place in the therapeutic armamentarium. Approaching therapy from the standpoint of physiology we can prevent ovulation and thus prevent painful menses. Although theoretically this sounds quite logical, from a practical point of view it is not usually as successful as one might expect. In our experience it has been difficult to prevent ovulation repeatedly in the normally ovulating woman. Although one ovulation can be prevented rather readily, the second is often extremely difficult to suppress with either estrogens or androgens, unless the dosage given is excessive (Fig. 1). Estrogens in the required dose range are prone to disturb the menstrual rhythm and cause menorrhagia, while androgens may cause masculinization, neither of which is a desirable side effect. Operative procedures, other than the time-honored dilatation of the cervix, for this relatively minor condition are generally to be discouraged. Presacral neurectomy is to be used only as a last resort and the results although frequently gratifying at the onset are often disappointing in the years following.(2)

With this relatively unsatisfactory armamentarium for the approach to the therapy of dysmenorrhea, a principle which would control the entire syndrome rather than single symptoms would therefore be most welcome. Hence, when an orally effective uterine relaxing factor (U.R.F.) was offered us for clinical testing on human beings it had enough points in its favor to warrant a trial.

In 1942, Falls and co-workers (3) reported the successful treatment of abortion with an aqueous extract of sow corpus luteum given intramuscularly. The action principle was therefore obviously not progesterone which is an alcohol-soluble, water-insoluble sterol. Krantz, Bryant, and Carr (4) in an effort to clarify the physiologically active principle, investigated the action of these aqueous extracts of sow corpora lutea on the isolated guinea pig uterus in situ and demonstrated the presence of a substance which possessed the ability to diminish the tone and abolish spontaneous muscular contraction. In the further identification of this substance, (5) it became apparent that it was closely related both chemically and in its biological activity

to a hormone described a number of years ago by Hisaw, (6) and designated as specific for the relaxation of the guinea pig symphysis. A chemical analysis by Felton and associates, (5) revealed that the uterine relaxing factor (U.R.F.) was, in addition to being water soluble, nondialyzable, heat stable, and destroyed by proteolytic enzymes and a variety of reducing agents. These properties seem to classify it as a protein or polypeptide.

Because of the ability of the hormone to produce uterine relaxation it seemed it might be of value in the treatment of dysmenorrhea. A report by Rezek (7) indicates that this is indeed possible. As an oral preparation is preferable to an intramuscular or intravenous one, experiments were designed to determine if there was any detectable relaxing activity in the blood serum after oral administration. Using the guinea pig as a test animal, it was found that 1 mg. of a typical sample of U.R.F. assayed 25 units per milligram, when tested by intravenous administration. The unit is "the minimal amount of substance which, when injected intravenously into the estrogenized virgin guinea pig, effects a 90 per cent reduction in the height of sponsaneous contractions for a period of at least 10 minutes." (5) The same material assayed 1.25 units per milligram when given by stomach gavage. The assay of the serum of 9 women who received the hormone orally is seen in Table I. Although the blood serum of normally menstruating women not under treatment has shown consistently negative titers, the serum of pregnant women usually has shown a positive titer. These blood level experiments in both animals and human beings indicate that the preparation was absorbed orally. In testing the toxicity of the drug, as much as 10,000 units in a single dose was given to 10 men with no untoward results. (8) Two women under observation have also taken 10,000 units at one time and, although they were somewhat drowsy for several hours, no other effects were observed.

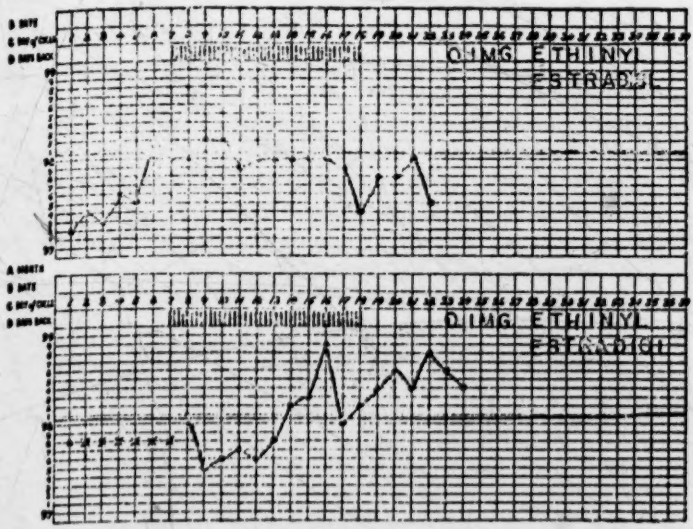


FIG. 1—Basal temperature chart of patient receiving estrogen. Ovulation is suppressed in the first cycle but there is a rebound phenomenon and ovulation occurs in spite of continued estrogen therapy in the second cycle.

TABLE I.—*Uterine relaxing factor in human serum after oral administration of lutrexin*

Patients	Control period [1] URF/cc serum	Units lutrexin given	Test period URF/cc serum ½ hour after administration
1	None	1, 500	1 unit.
2	None	1, 500	None.
3	None	1, 500	1 unit.
4	None	1, 500	Trace.
5	None	1, 500	½ unit.
6	None	3, 000	1 unit.
7	None	3, 000	None.
8	None	3, 000	¾ unit.
9	None	3, 000	1½ unit.

[1] Blood specimens drawn before Lutrexin was given.

CLINICAL MATERIAL

In the present study 90 women who complained primarily of painful menstruation have been treated with tablets of U.R.F.* They were all intelligent women, capable of evaluating the results, chiefly nurses, technicians, and aides on the hospital staff. No effort was made at the onset of treatment to differentiate the etiological factors of the dysmenorrhea. All had had some medication during previous periods of dysmenorrhea. None were told the nature of the new drug or what to expect in the way of amelioration of their symptoms except that the drug has been beneficial in tests elsewhere. Tablets were supplied in 500 and 1,000 units doses. Specific directions were given as to how and when they were to be taken. Only enough calculated for the current period and the ensuing one were given so that the patients would have to return for succeeding doses and to report on the results obtained.

CLINICAL RESULTS

Of the 90 women in this series 47 had consistently good results with adequate dosage. Fourteen women had partial relief of symptoms, making a total of 61 patients with satisfactory response to therapy. Twenty-nine had no relief; 8 of these women were considered to be inadequately treated and were lost to follow-up examinations when attempts were made to locate them for re-treatment with increased dosage during a subsequent menstruation.

The 47 patients with good results included 24 women who received medication during more than one menstrual cycle. Ten patients were relieved of symptoms by an initial dose of 1,000 units and 1,000 units every 2 to 4 hours. One patient was relieved by an initial dose of 1,500 units, 3 required 2,000, and 29 required 3,000 units with an additional 1,000 units every 2 to 4 hours. One patient required 3,500 units. Seven women were unrelieved by 1,000 or 2,000 units but found 3,000 units were effective.

The group of 14 women who were classified as receiving fair results from medication were sufficiently relieved of symptoms to continue their duties but were still not completely free of discomfort. Two of these women took only 1,000 units at onset

* Lutrexin—Hynson, Wescott & Dunning, Inc.

of therapy and could not be persuaded to increase their dosage in an effort to obtain additional relief. Four have taken 1,000 units, two 2,000 units, and two 3,000 units during a single menstrual cycle. Three patients in this group have also had improved results with increased dosage.

Of the 29 women who were considered therapeutic failures, 10 were unavailable for follow-up study. Two of these 10 patients were adequately treated and the remaining 8 are to be considered inadequately treated as they received an initial dose of only 1,000 units with 1,000 units every 2 to 4 hours thereafter. Sixteen of the 19 remaining women who took medication two or more times without relief all received 3,000 units initially or during the second month of therapy. An effort was made to evaluate the pelvic findings and etiological factors contributing to the dysmenorrhea in this group of patients. Nine women were found to have normal pelvic structures, 3 had retroverted uteri and associated menorrhagia. Three had pelvic inflammatory disease, 1 had a myomatous uterus and menorrhagia, 2 had the Stein syndrome, 1 had dwarfism of the achondroplastic type with an infantile uterus, and 2 had severe vaginitis. One had menorrhagia associated with severe hyperthyroidism. However, although the patient is now in a euthyroid state on propylthiouracil medication, she still has excessive bleeding and dysmenorrhea. She obtained some relief if she was able to take her medication before the actual onset of severe cramps. But as she was often awakened from a sound sleep by menstrual cramps, this was frequently impossible. On occasions when it was possible to prevent ovulation with estrogens this patient had no pelvic discomfort. It is of interest that the dysmenorrhea of the achondroplastic dwarf was also relieved by prevention of ovulation. Seven patients refused pelvic examination. Six women in the group were thought to have rather severe anxiety neurosis with associated tension states in addition to other findings.

No side reactions were noted in any of the cases treated. One factor which contributed to the unwillingness to try larger doses was the number of pills to be ingested. In order to overcome this, future use of the drug will employ the tablets of larger unit content. It is also planned to run a concomitant control series by using placebos made up in exactly the same size and configuration. This necessitated the manufacturing of a special pill as the U.R.F. gives the tablet a brown-speckled appearance

which is not easily disguised. Like all therapy for dysmenorrhea, U.R.F. seemingly worked better when given early, ideally the day before menses started, and certainly before cramps became severe or nausea occurred.

SUMMARY

A uterine relaxant, a factor obtained from the corpus luteum of sow ovaries, has been isolated and the bio-assay standardized. It has been chemically classified as a protein or polypeptide. This substance is not destroyed in the stomach as the active principle appears in the blood serum within 30 minutes after oral administration in the human being. In a series of 90 women who complained of dysmenorrhea an initial dose of 1,000 to 3,000 units followed by 1,000 units every 2 to 4 hours was sufficient to control the symptoms of 61 women. Twenty-nine women had no results from therapy, but only 21 were considered adequately treated. Although the efficiency of medication for dysmenorrhea is notoriously difficult to evaluate, the fact that a number of women obtained no relief from small doses but adequate relief when larger amounts of U.R.F. were administered leads us to believe that the action is physiological rather than psychological. It seems from this preliminary survey that the uterine relaxing factor is of value in the treatment of dysmenorrhea as it relieves the entire symptom complex and has no sedative effect. It is apparently ineffective in those women with major psychosomatic difficulties or anatomically abnormal pelves. Ftrther studies are plannet using larger doses as well as a control series making use of a placebo tablet similar in all respects to those containing U.R.F.

CONCLUSIONS

A new drug, capable of acting against dysmenorrhea and to be given orally, has been subjected to limited preliminary clinical tests. It shows enough satisfactory results to warrant its use. Studies will be continued to evaluate it further, especially to determine the optimal dosage.

REFERENCES

1. Miller, N. F., and Berhman, S. J.: Am. J. Obst. & Gynec. 63: 505, 1953.
2. Rutherford, Robert N.: West J. Surg. 50: 598, 1942.
3. Falls, F. H., Rezek, George H., and Bennensohn, S. J.: Surg., Gynec. & Obst. 75: 289, 1942.

4. Krantz, J. C., Bryant, H. H., and Carr, C. J.: Surg., Gynec. & Obst. 90: 372, 1950.
5. Felton, Lloyd C., Frieden, Edward H., and Bryant, Harold H.: J. Pharmacol. & Exper. Therap. 107: 160, 1953.
6. Hisaw, F. L.: Proc. Soc. Exper. Biol. & Med. 23: 661, 1926.
7. Rezek, George H.: In press.
8. London, Frank: Personal communication.

Lututrin: A New Drug for Relief of Dysmenorrhea

(SCOTT S. JONES, M.D., TACOMA, WASHINGTON)

Lututrin (LUTREXIN®) *Protein-like substance extracted from ovarian tissue, which may be a new hormone, has given relief in 87 per cent of 40 cases.*

Dysmenorrhea is defined as painful menstruation, but actually is a symptom complex of abdominal cramps, backache, leg ache, headache, diarrhea, nausea and vomiting, and general malaise, occurring at the time of the menstrual period, and of varying degrees of severity.

There are as many or more kinds of treatment as there are symptoms. Physical and mental hygiene, exercise, heat, analgesics, hypnotics, smooth muscle relaxants, narcotics, endocrines, stem passaries, cervical dilatation, even presacral neurectomy. We have tried them all, with some success and many failures.

One can usually obtain a painless period by means of preventing ovulation with estrogens or androgens. But you cannot continue preventing ovulation month after month and you should not so upset the menstrual rhythm.

CHEMICAL AND MECHANICAL AIDS

In the field of drugs, I have had the best success with a combination of atropine, papaverine, aspirin, phenacetin and camphor monobromate. In some cases of severe cramps, I have had a measure of success with the flexible stem pessary. This is inserted in the office without anesthetic. It stimulates the uterus to react to the presence of a foreign body with strong contractions which, over a period of several weeks, result in increased vascularity of the myometrium. Not all cases respond and a certain amount of cervicitis is produced by the pessary.

Read before meeting of Pacific Northwest Obstetrical and Gynecological Society at Victoria, B. C., May 18, 1955.

One hates to advise presacral neurectomy unless some other condition warrants operation. In spite of Cotte's report of excellent results, others have been unable to duplicate them. Even when relief is obtained, in some cases it has not been lasting. Hysterectomy is reserved for the older patient and one hesitates to remove a normal uterus for the symptom of pain alone.

Lututrin

Recently, I have been using a new drug called lututrin with excellent results in severe dysmenorrhea. This is a uterine relaxing factor obtained from the corpus luteum of sow overies and standardized for potency in terms of units of activity on the guinea pig uterus.*

In 1942, it was found that uterine contractions stimulated by 1 cc. of pituitrin could be stopped within 25 minutes by giving 10 cc. of aqueous lutein. This was not due to progesterone, so the presence of some unidentified substance was suspected.

In 1950, Krantz, Bryant and Carr [1] used a new method of assay. A guinea pig was given estrogens for 12 days, the uterus was exposed and attached to a kymograph and the material to be tested was injected into the jugular vein.

Using this method, Rezek [2] found that a substance obtained from corpus luteum contained a uterine relaxing factor which was effective in inhibiting contractions of the uterus. It was so extremely potent that 0.002 mg. produced definite relaxation. This gives a direct method of assay of potency of the substance, which is a water soluble non-steroid. In 1952, Felton, Frieden and Bryant [3] established the fact that it is protein type of compound, or polypeptide. Years ago, Hisaw [4] had found another factor on ovarian substance, called relaxin, which has the

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* Marketed by Hynson, Westcott and Dunning under the trade name, Lutrexin.

[1] Krantz, J. C., Jr., Bryant, H. H., and Carr, C. J., Action of aqueous corpus luteum extract upon uterine activity, Surg., Gynec. and Obst. 90:372-375, (March) 1950.

[2] Rezek, G. H., Effect of a new potent uterine relaxing factor of the corpus luteum in treatment of dysmenorrhea. Am. J. Obst. and Gynec. 66: 396-402, (Aug.) 1953.

[3] Felton, L. C., Frieden, E. H., and Bryant, H. H., Effects of ovarian extracts upon activity of guinea pig uterus in situ, J. Pharmacol. and Exper. Therap. 107:160-164, (Feb.) 1953.

[4] Hisaw, F. L., Experimental relaxation of the pubic ligament of the guinea pig. Proc. Soc. Exper. Biol. and Med. 23: 661-663. (May) 1926.

property of relaxing the symphysis pubis of the guinea pig. The two substances are not identical.

The relaxing factor discovered by Rezek is not destroyed in the stomach. The active principle appears in the blood serum within 30 minutes after oral administration in the human.

Lutrexin comes in tablets of 1,000 unit strength. It appears to be non-toxic. Doses of 10,000 units have been given to both males and females without any untoward symptoms. The usual dose is 2,000 to 4000 units when the cramps first begin, or even before they begin if the patient has any warning. One of three tablets may be given every 3 to 4 hours if necessary and as long as needed to keep the patient free of cramps. At first, I had a tendency to give too small a dose but I do not hesitate to give 4 tablets as the first dose now and in so doing have had much better results.

CLINICAL TRIAL

My associate and I have now treated approximately 40 cases of severe dysmenorrhea with lututrin. These were cases without other demonstrable disease. Results were classified as excellent when all symptoms were relieved, good when cramps were much abated and the patient was able to go about her work, fair when there was slight relief only, and poor when no relief was obtained. Using this classification, we had 23 or 57.5 percent excellent, 12 or 30 percent good, 2 fair and 3 poor. One said it made her feel worse. Thus, it can be seen that 87.5 percent of cases were greatly benefited. This is better than results I have had with any other type of treatment.

Jones and Smith[5] have reported a series of 90 women with pain controlled in 61. They had 21 which they considered adequately treated that had no results from the medication. Many of these had pelvic disease which contributed to the dysmenorrhea. Six were thought to have rather severe anxiety neurosis.

ANALYSIS OF FAILURES

I have attempted to evaluate our 5 cases of fair or poor results. It seems to me that there was some mental factor contributing to the dysmenorrhea. They rather considered themselves martyrs, and expected sympathy for their troubles.

[5] Jones, G. S., and Smith, F., Treatment of dysmenorrhea symptom complex, Am. J. Obst. and Gynec. 61:628–633, (March) 1954

One was led to believe by her mother that her trouble was the cross she had to bear for being a woman. The first period she was given two tablets at the onset of pain and got little relief. The second period she took three tablets and had only a few cramps. Thereafter she took four tablets but this medication had lost its newness by that time and had no appreciable effect.

Another was a 32 year old school teacher. She was given three tablets at once. There was no lessening of the cramps but she said she had been chilled when her period started and she wanted to try them again. The next period she took four tablets but there was no diminution of the pain. I cannot account for this failure. She was a very intelligent woman, with no apparent conflicts.

The patient whose cramps were made worse was 40 years old and had two children, 13 and 12 years old. She had always had painful periods and was very nervous at all times. Her blood pressure ranged from 150/80 to 160/90. Her uterus was very firm and slightly larger than normal for a multipara. This may have been a fibrous uterus but I attribute failure to her highly nervous state.

GRATITUDE

What about the patients who are relieved by the medication? They are extremely grateful. One girl was having her prescription renewed so frequently that I asked her about it. It seems that she was going to the University and could not bear to see her sorority sisters suffer so she was administering Lutrexin to them.

I would like to quote from a letter I received from a 44 year old woman visiting from Minnesota, who had had severe cramps since puberty, despite having a child of 12. She received some relief from androgrens. She says, "I think we have discovered a miracle. I am better than at any time in the past ten years. The darn stuff is funny—I will think on the second or third day that I am completely over my difficulties, and more or less forget it. Then I will suddenly be hit with severe cramps and the accompany nausea, etc. I run like crazy and take two tablets, and within an hour feel like a new woman. The druggist here had never heard of it, but my doctor had him order it, and upon my report is prescribing it for all his patients with such complaints, and I am sure they are as grateful as I."

Even those who are not completely relieved come back for more tablets when they go through a period without them. That, to me, is the best proof that they are obtaining some benefit.

I believe that this medication deserves more exhaustive trials.

[Reprinted from Northwest Medicine, Vol. 54, pp. 1253–1254, November, 1955—Printed in U.S.A.]

[Reprinted from *Annals of The New York Academy of Sciences*, Volume 75, Article 2 Pages 1037–1038, January 9, 1959]

HAROLD H. BRYANT (*Hynson, Westcott & Dunning, Inc., Baltimore, Md.*)

The procedure used for biological assay and standardization of Lutrexin* is strictly an *in vivo* method. The test is designed to ascertain the amount of uterine-relaxing hormone present and is not a procedure suitable for assay of relaxin per se. While it is true that Lutrexin preparations do contain some relaxin, the Lutrexin assay procedure will not, and does not, serve as a suitable means of assay of the amount present.

Furthermore, the Lutrexin assay method is not a "uterine strip" or excised muscle procedure. The test involves the entire animal, as the uterus is completely intact with full nerve and blood supply. The material being assayed is injected intravenously or administered orally. In the routine assay, the test material is injected intravenously because of the sharp end point obtained following this route of administration. To anyone familiar with the problems of biological standardization, the desirability of a sharp end point is obvious. The accuracy of a bioassay is directly proportional to the sharpness of a pharmacological response being observed. However, the Lutrexin preparation is also administered orally, and the pharmacological response in decreased uterine activity is readily apparent. The dosage is, of course, higher, and the effect is not as quickly apparent, as is true of all pharmacological agents. The dose required for clinical effectiveness has been determined by the physician administering the drug orally. The laboratory assay of the drug simply determines and standardizes the potency to enable the clinician to administer a "known" amount.

* Hynson, Westcott & Dunning, Inc., Baltimore, Md.



FIGURE 1. Photographs of assay tracings demonstrating the response to intravenous (a) and orally (b) administered Lutrexin. Note the sharp end point following intravenous injection. Also, observe the effective inhibition of uterine activity following oral administration.

The uterine strip is of very limited value, especially with the water-soluble hormones of the ovary. The original publication (Krantz *et al.*, 1950) describing the assay procedure noted that 15 of 26 substances studied, using excised uterine strips, brought about a diminution of uterine activity. The uterine strip is then completely nonspecific and not suitable for assay purposes.

The *in vivo* relaxation of the intact uterus by the ovarian extract has proved to be quite specific. Roughly one hundred substances studied during the past ten years using the Lutrexin assay procedure have failed to give similar inhibition of uterine activity (FIGURE 1).

REFERENCE

KRANTZ, J. C., Jr., H. H. BRYANT & C. J. CARR. 1950. The action of aqueous corpus luteum extract upon uterine activity. Surg. Gynecol. Obstet. 90: 372–375.

United States Court of Appeals for the Fourth Circuit

No. 71-1717

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, PETITIONER

v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, RESPONDENTS

On Petition to Review an Order of the Commissioner of Food and Drugs

Argued February 7, 1972. Decided May 24, 1972.

Before BUTZNER, RUSSELL AND FIELD, *Circuit Judges.*

Edward Brown Williams (Jan Edward Williams and Harter, Calhoun and Williams, Robert H. Patterson, Jr., and McGuire, Woods and Battle, and John Kyle Warley on brief) for Petitioner, and Gregory B. Hovendon, Attorney, Department of Justice, (Richard W. McLaren, Assistant Attorney General, and Peter Barton Hutt, Assistant General Counsel, Food, Drugs and Environmental Health Division, Eugene M. Pfeifer, Attorney, United States Department of Health, Education, and Welfare, on brief) for Respondents. Joel E. Hoffman (Robert L. Wald, Selma M. Levine, and Wald, Harkrader and Ross on brief) for Amicus Curiae.

RUSSELL, *Circuit Judge:*

The appellant, a drug manufacturer, seeks review of a final order withdrawing marketing approval (NDA) of the drug Lutrexin by the Commissioner of Food and Drugs, Department of Health, Education and Welfare.[1] The appellant alleges error in such order of withdrawal (1) for failure to sustain its claim of exemption from withdrawal on account of lack of "substantial evidence" of effectiveness of its drug and, if this claim of exemption is overruled, (2) for denial of a hearing, as required under the applicable statute, on its showing of effectiveness. We reverse.

[1] Section 355(h), 21 U.S.C.

The appellant was granted an approved NDA for Lutrexin in 1952. At that time, the Food, Drug and Cosmetic Act of 1938 conditioned such grant on general recognition of safety of the drug approved. In 1962 the Act was amended to authorize withdrawal of an approved NDA for any drug for which the Commissioner "after due notice and opportunity for hearing", found there was "a lack of substantial evidence of effectiveness." [2] The term "substantial evidence" was defined in the Amendments as "consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." [3] There was an exemption from these requirements for drugs, which, *inter alia*, were not covered on the day immediately before the enacting date of the Amendments (i.e., October 9, 1962) by an "effective NDA".[4]

In carrying out his new responsibilities under the Amendments, the Commissioner secured the services of the National Academy of Sciences-National Research Council (NAS–NRC) for reviewing the claims of effectiveness on behalf of any drugs NDA'd between 1938 and 1962.[5] To facilitate its assignment, NAS–NRC set up a Drug Efficacy Study Group and all drug manufacturers with approved NDAs obtained between 1938 and 1962 were directed by the Commissioner to submit to this Group evidence "pertinent to the evaluation of the effectiveness of the(ir) drugs" [6] The appellant submitted to the Group clinical data, investigations and studies in support of the ef-

[2] Section 355(e), 21 U.S.C.

[3] Section 355(d), 21 U.S.C.

[4] "In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force * * *, and (C) was not covered by an effective application under section 505 of that Act * * *, the amendments to section 201(p) * * * made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day." Section 107(c)(4), appended to Section 321, 21 U.S.C. 1972 Supplement, p. 192.

[5] F.R. 13014, October 6, 1966.

[6] 21 F.R. 13014.

fectiveness for its drug Lutrexin After considering such data, NAS–NRC concluded that Lutrexin was "possibly effective" but indicated the supporting documentation was inadequate.

The Commissioner advised the appellant of his concurrence with the conclusions of NAS–NRC and, as required by the statute, extended to it an opportunity for a hearing on the proposed withdrawal of the approved NDA for Lutrexin.[7] At such a hearing, the appellant was advised it might "produce evidence and arguments why approval * * * should not be withdrawn." [8] The appellant in due time requested such hearing. Under the Commissioner's regulations, a hearing was required within 90 days after such request, unless the parties agreed otherwise.[9] However, although no delay was agreed on, hearing within such period was not had. The delay on the part of the Commissioner in setting a hearing was due to litigation over the procedure to be followed by it in implementing its efficacy review and in conducting hearings resulting therefrom.[10] It is unnecessary to review the difficulties encountered in developing valid regulations for such hearings. It is sufficient for the issues here that it was not until May 8, 1970, but that the legal objections to the regulations were finally resolved.

During this interregnum when the regulations of the Agency were under challenge and the Commissioner was delaying a hearing, the appellant, whose request for a hearing had been delayed for more than a year, sought in District Court a declaratory judgment to the effect that, under the exemption clause included in the 1962 Amendments, Lutrexin was not a "new drug" on and before October 10, 1962, and was thereby exempt from the requirement of evidence of effectiveness under the Amendments. Such action was dismissed on the ground that primary jurisdiction to resolve the issue of exemption under the Act rested with the Commissioner. No appeal was taken from this dismissal.

While this declaratory action was pending, the Commissioner issued his new regulations detailing the circumstances under which an applicant might secure a hearing on a proposal by the Commissioner for withdrawal of an effective NDA. By

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[7] 33 F.R. 7701.

[8] 34 F.R. 5556.

[9] 21 C.F.R. 130.14(b).

[10] See *Pharmaceutical Manufacturers Association* v. *Finch* (D.C.Del. 1970) 307 F. Supp. 858; *Upjohn* v. *Finch* (6th Cir. 1970) 422 F. 2d 944; and *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536.

these regulations, the Commissioner was authorized to deny a hearing, "when it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data".[11]

After the regulation had been legally promulgated, which was more than a year after the appellant had requested a hearing, the Commissioner directed the appellant's attention to these new regulations and suggested that it amend its request for a hearing to comply. Though it contended it had, by its earlier request, perfected its right to a hearing and was not obligated to amend its request, the appellant did, following the dismissal of its declaratory action, submit a considerable amount of clinical medical studies and investigations in support of the claim of effectiveness for its product by way of compliance with the new regulations. The Commissioner, however, dismissed the appellant's request for a hearing on the basis of such showing, finding (1) that its drug was a "new drug" requiring proof of effectiveness, and (2) that its showing of effectiveness was insufficient to demonstrate a "genuine and material issue of fact" under the test of "substantial evidence" as defined in the Amendments. On the basis of these findings it withdrew the approved NDA for Lutrexin. It is from this order that appeal has been taken.

I

The appellant's claim to an exemption for its drug is easily disposed of. We have held in a related case that a drug covered by a pre-1962 approved NDA, which had not been withdrawn under the procedure set forth in Section 505(e), is not entitled to the exemption granted under Section 107(c)(4) of the Amendments.[12] The appellant's NDA was outstanding and had not been legally withdrawn on October 10, 1962. It cannot ac-

[11] 21 C.F.R. 130.14(b).

[12] *USV Pharmaceutical Corp. v. Richardson*, (4th Cir. 1972) ——— F. 2d ———.

cordingly claim the benefit of the exemption statute for its drug. While the appellant was entitled to have this issue resolved by the District Court, it was not prejudiced by, and cannot complain of, the refusal by the District Court to exercise jurisdiction. Nor, for that matter, did the appellant appeal and is accordingly without standing in this proceeding to challenge that dismissal.

II

The crucial issue in this case, however, is posed by the appellant's second contention and revolves about the requirement in the Act that, before the entry of a final order of withdrawal, the applicant be given an "opportunity for hearing". At such a hearing, the procedure adopted by the Commissioner allows the applicant to "produce evidence and arguments to show why approvals of (its drugs) * * * should not be withdrawn." [12a] Of course, the Commissioner might, as he did by his regulations issued in 1970, provide for the denial of a hearing where it clearly appeared from the applicant's own showing there was no "genuine and substantial issue of fact" on which the claim of the applicant might be sustained, *Ciba-Geigy Corp.* v. *Richardson* (2d Cir. 1971) 446 F. 2d 466, 468. It may be assumed that such regulation, when issued will apply to all pending applications. *U.S.* v. *Storer Broadcasting Co.* (1956) 351 U.S. 192, 205. But, in applying this regulation and in making his determination thereunder, the Commissioner's discretion is not absolute. Neither due process nor the Administrative Practice Act permits an arbitrary denial in any case where it can be fairly said there are "genuine and substantial issues of fact" in dispute.[13]

Such a denial would, in addition, be violative of the Congressional purpose expressed in the provision for a hearing. And the courts must see that such Congressional purpose is not thwarted by administrative usurpation; or, as the Court said in *Environ-*

[12a] Whether this is too narrow and improperly confines the scope of the hearing, so far as it is adjudicatory, see Davis, *The Requirement of a Trial-Type Hearing*, 70 Har. L. Rev. 193 (1956).

[13] See *Ciba-Geigy Corp.* v. *Richardson*, *supra*, at p. 468. The question is analogous to that presented by a demand for a hearing in connection with an N.L.R.B. election where the right to a hearing subject to the same general limitations as stated in the Commissioner's regulations, and it would seem the same test of the right to a hearing is applicable. For the rule in such N.L.R.B. case, see *N.L.R.B.* v. *Bata Shoe Co.* (4th Cir. 1967) 377 F. 2d 821, 825-6; *United States Rubber Co.* v. *N.L.R.B.* (5th Cir 1967) 373 2d 602, 606; *N.L.R.B.* v. *Smith Industries, Inc.* (5th Cir. 1968) 403 F. 2d 889, 892-5.

mental Defense Fund, Inc. v. *Ruckelshaus* (D.C.C.A. 1971) 439 F. 2d 584, 596, the courts have "an obligation to ensure that the administrative standards conform to the legislative purpose* * *." Accordingly, only if it can be fairly said that the clinical tests and medical studies and investigations submitted by the applicant, if credited and accepted, will not support a finding that they provide "substantial evidence" of effectiveness was it proper for the Commissioner to deny the appellant a hearing *before* entering a final order of withdrawal. The judicial test is somewhat the converse of that to be applied in a review of a decision of the Commissioner entered *after* a hearing. In that instance, his decision is to be upheld, if sustained by any substantial evidence.[14] But in determining whether the Commissioner acted within the limits of his discretion on the procedural question of whether a hearing is to be allowed, the test is whether there is any "genuine and substantial" evidence that supports the position of the applicant.

Manifestly, the applicant does not have to satisfy or convince the Commissioner by his evidence that his product is effective as a predicate for securing his right to a hearing. If that was his burden, a hearing would never be necessary or appropriate. If he, by his showing, convinced or satisfied the Commissioner, the proposed withdrawal would naturally be denied; on the other hand, if he failed to satisfy, then the Commissioner would deny a hearing and order withdrawal. In either event, a hearing would be useless and the Congressional promise of a hearing would be purely illusory. No such exacting standard of proof is required as a basis simply for the right to be heard; as has been observed, all that is required for securing a right to a hearing is that the showing be such that, if accepted, a finding of "substantial evidence" of effectiveness would be supportable. And "substantial" in this connection does not mean "preponderant evidence" or "conclusive evidence". Congress specifically discarded those terms for the milder term "substantial," which was understood to embrace the idea, not of a preponderance but rather of a responsible body of qualified opinion.[15]

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[14] Section 355(h), 21 U.S.C.

[15] In the course of committee deliberation a distinction evolved * * * between two tests the "preponderant evidence" test and the "substantial evidence" test as now specifically defined. Under the former a claim would not be accepted under the new drug section unless it represented the pre-

Applying the foregoing principles, we are of opinion the showing of the appellant was such that, under a reasonable construction of the Commissioner's own regulations, as well as under familiar principles of due process, and the requirements of the Administrative Procedure Act, it was entitled to an impartial hearing before its NDA was withdrawn. It must be noted that no qualified expert has given an opinion that Lutrexin is ineffective for the uses intended. The NAS–NRC review concluded it was "possibly effective". Neither is there any contention that it is unsafe when used for the purposes intended. The real basis for the determination by the Commissioner that the appellant had failed to make a showing of any genuine issue of fact on the effectiveness of its drug was the conclusion that the various scientific articles and tests submitted by the appellant were not "adequate and well-controlled clinical investigations" within the statutory definition of "substantial evidence". In his decision, the Commissioner sought to point out the deficiencies in the investigations submitted by the appellant which justified this conclusion. In so doing, he did not impugn the competency or qualifications of the scientists and medical experts whose investigations were cited by the appellant in support of its claim. Their professional qualifications, as they appear in the record, are impressive. Their investigations and opinions, some of which have been published in recognized professional medical journals, are, however, dismissed by the Commissioner with the statement that, "No adequate and well-controlled clinical investigations published in the medical literature had been identified."

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ponderant view of experts * * * the committee recognizes that in the difficult area of drug testing and evaluation there will frequently, if not usually, be a difference of responsible opinion. The committee feels the existence of such a difference should not result in disapproval of a claim of effectiveness if it is supported by substantial evidence defined in the manner set forth below [that is adequate and well controlled investigations by qualified experts upon the basis of which conclusions made be fairly and responsibly drawn.].

[Application of the substantial evidence test means that] a claim could be rejected if it were found (a) that the investigations were not "adequate"; (b) that they were not "well-controlled"; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which its application is made; or (d) that the conclusions to be drawn by such experts could not fairly and responsibly be derived from their investigation.

S. Rep. No. 1744, 87th Cong., 2nd Sess. Part II, pp. 5–6, and see, 2 U.S. Code Congress. & Administrative News, 87th Cong., 2d Sess., p. 2892 (1962).

In making that statement, he disregards the categorical opinion of his former Director of the Bureau of Medicine and Medical Director that the clinical tests and investigations submitted by the appellant represented " 'well-controlled' clinical studies". He proceeds to fault two investigations published in an authoritative medical journal, submitted by the appellant, because, "There is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced", and "There is no summary or explanation of the statistical methods used in analysis of the data to show that results were not biased or due to chance". Another unpublished investigation is dismissed because, "Substantiating documentation to establish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided". Two published studies by a clinical professor of Obstetrics at the University of Illinois are criticized, in one instance, because "The report does not state the method of patient selection" and "Concomitant medication is not excluded" and, in the other, because "The method of selection of the patients does not show progressive dilation of the cervix, which is necessary to accurately diagnose premature labor."

Assuming that all the objections by the Commissioner to these clinical studies, conducted as they were by competent medical authorities, may have some validity, they do not justify a final conclusion, made *ex parte*, without a hearing, that it "clearly appears" that there is no genuine issue of fact on the effectiveness of Lutrexin, which is the test under the Commissioner's own regulation for denial of a hearing; at most, they merely create a genuine question of fact to be resolved at a hearing upon proper evidence. Whether the studies were as controlled as they might have been and whether there was a failure in these studies as published to fill in all the details the Commissioner might think appropriate are matters that could be developed at a hearing, after the authors were examined and the reliability of the investigations further inquired into.

The order of the Commissioner, from which this appeal is taken, is set aside for failure to provide the petitioner with an "opportunity for a hearing" before the entry of said order.

Reversed.

United States Court of Appeals for the Fourth Circuit

No. 71-1717

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, PETITIONER

v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, RESPONDENTS

On Petition to Review on Order of the Commissoiner of Food and Drugs

THIS CAUSE came on to be heard upon the petition of Hynson, Westcott and Dunning, Incorporated, for review of an order issued against it by Elliot Richardson, Secretary of Health, Education, Welfare, and Charles C. Edwards, Commissioner of Food and Drugs, on May 31, 1971, in proceedings before the said Agency; and upon a certified list in lieu of a transcript of the record; and the said cause was argued by counsel.

ON CONSIDERATION WHEREOF, it is ordered, adjudged and decreed by the United States Court of Appeals for the Fourth Circuit, that the order of the Commissioner, from which this appeal is taken, is set aside for failure to provide the petitioner with an "opportunity for a hearing" before the entry of said order. The order is reversed.

A True Copy, Teste:
Filed May 24, 1972.

SAMUEL W. PHILLIPS,
Clerk.

By J. U. LAYARD,
Deputy Clerk.

In the Supreme Court of the United States

No. 72–394

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE, ET AL., PETITIONERS,

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

ORDER ALLOWING CERTIORARI. Filed January 8, 1973

The petition herein for a writ of certiorari to the United States Court of Appeals for the Fourth Circuit is granted. The case is consolidated with Nos. 72–414, 72–528, 72–555, and 72–666, and a total of three hours is allotted for oral argument.

In the Supreme Court of the United States

No. 72–414

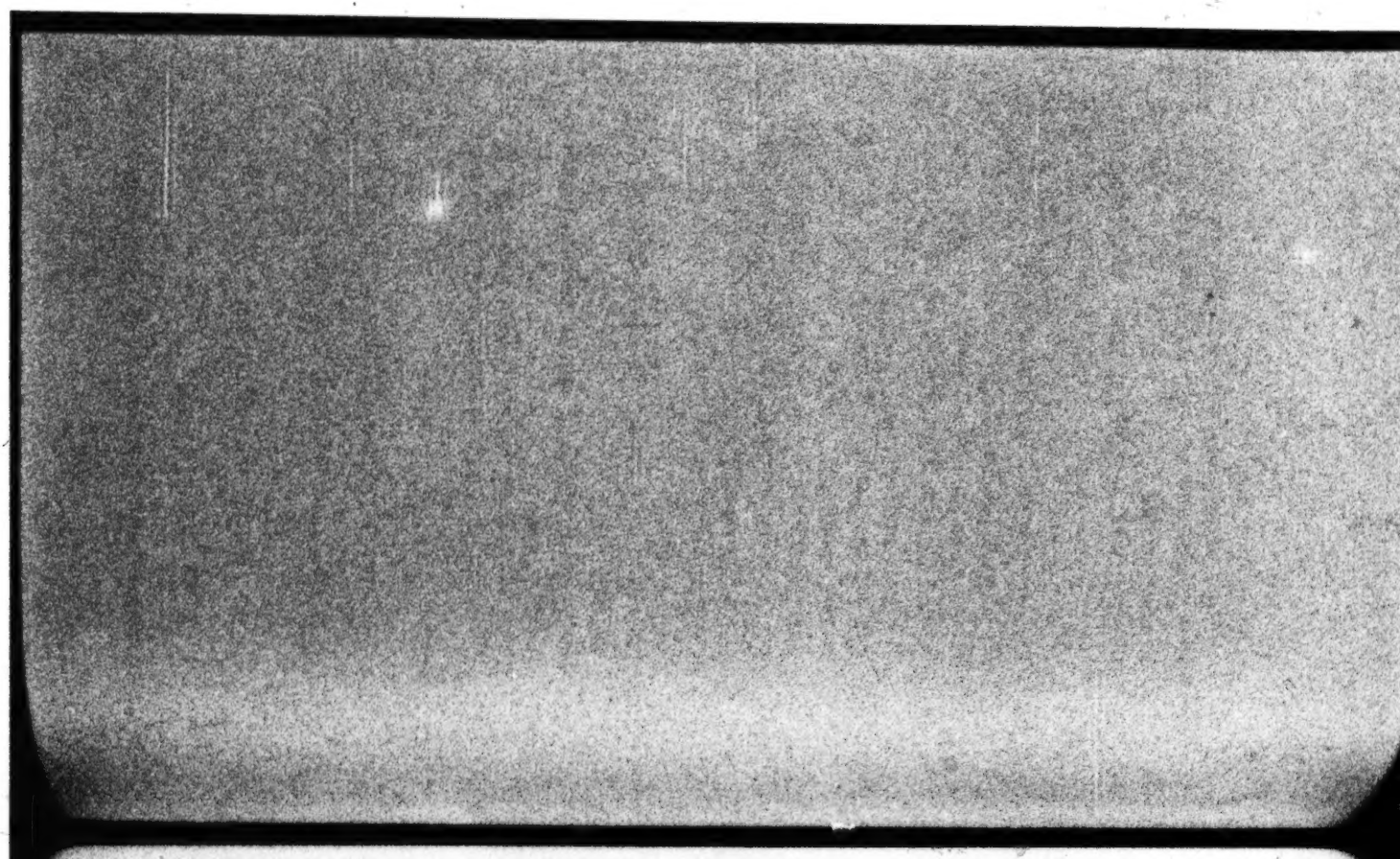
HYNSON, WESTCOTT AND DUNNING, INCORPORATED, PETITIONER,

v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE, ET AL.

ORDER ALLOWING CERTIORARI. Filed January 8, 1973

The petition herein for a writ of certiorari to the United States Court of Appeals for the Fourth Circuit is granted. The case is consolidated with Nos. 72–394, 72–528, 72–555, and 72–666, and a total of three hours is allotted for oral argument.



In the United States Court of Appeals for the Third Circuit

(No. 71–1512)

CIBA CORPORATION, APPELLANT

v.

ELLIOT L. RICHARDSON, ET AL., APPELLEES

RELEVANT DOCKET ENTRIES

Date		
1971		
June	15	Copy of Notice of Appeal rec'd. May 21, 1971, filed. Record rec'd. June 8, 1971 (except Paper No. 5), filed.
		Appearance of Clyde A. Szuch, Esquire for appellant, filed.
July	19	Appearance of Howard S. Epstein, Esquire for appellees, filed.
July	26	Brief and appendix for appellant, received and filed. (25 copies).
Aug.	27	Brief for appellee, filed. (and appendix rec'd for the information of the Court.) Certificate of service attached.
Sept.	9	Certificate of service of appellant's brief and appendix by mail on July 26, 1971, filed. (2 copies).
Sept.	14	Consent motion by appellant for leave to file reply brief out of time to September 30, 1971, filed. (4 copies). Certificate of service attached.
Sept.	17	Above consent motion granted. *Clerk.*
1972		
Apr.	11	Argued. Coram: Hastie, Van Dusen and Aldisert, Circuit Judges.
May	30	Letter dated May 26, 1972 rec'd from Clyde A. Szuch, Esquire for the information of the Court.

Date		
1972		
June	5	Opinion Per Curiam (*Hastie*, Van Dusen and Aldisert, Circuit Judges), filed.
June	5	Judgment affirming the judgment of the District Court filed March 10, 1971, with costs taxed aganist appellant, filed.
June	16	Letter, dated June 14, 1972, from Cheryl S. Karner, Esquire, counsel for appellee advising that the Department of Justice intends to waive the costs in this case, filed.
June	27	Certified judgment in lieu of formal mandate issued.
June	27	Record returned to Clk of D.C.
June	29	Receipt for record, filed.
Oct.	6	Notice of filing of petition for writ of certiorari on Oct. 2, 1972 rec'd from Clerk of S.C. (S.C. No. 72–528), filed.
1973		
Jan.	16	Certified copy of order dated Jan. 8, 1973 rec'd from Clerk of Supreme Court and advising this case is consolidated with Nos. 72–394, 72–414, 72–555 and 72–666, and granting petition for writ of certiorari, filed. (S.C. No. 72–528)
Feb.	6	Certified copy of appendix and proceedings in this Court forwarded to the Clerk of the Supreme Court pursuant to their request (see letter dated January 29, 1973).

In the United States District Court, District of New Jersey
Civil Action No. 1210–70

CIBA CORPORATION, A CORPORATION OF THE STATE OF DELAWARE, PLAINTIFF,

vs.

ELLIOTT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE AND DR. CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, DEFENDANTS

COMPLAINT

Ciba Corporation, a corporation of the State of Delaware, having its principal place of business at 556 Morris Avenue, Summit, New Jersey, by way of Complaint, says

FIRST COUNT

1. This action arises under the Federal Food, Drug and Cosmetic Act of 1938 as amended, 21 U.S.C. § 301 et seq. (hereinafter the "Act"), the Drug Amendments Act of 1962, 76 Stat. 780 (1962) and § 9 of the Administrative Procedure Act, 5 U.S.C.A., § 558, and involves an amount in controversy in excess of $10,000. There exists between the parties an actual controversy, justiciable in nature, as to which plaintiff requires a declaration of its rights by this Court. This Court has jurisdiction of this cause pursuant to the provisions of Title 28 U.S.C.A. §§ 1331, 1337 and 2201–02 and Title 5 U.S.C.A. §§ 701–706.

2. Ciba Corporation is engaged in the manufacture and distribution in interstate commerce of "drugs" as that term is defined in the Act, including a drug marketed under the brand name "Ritonic".

3. Defendant Elliott L. Richardson is the Secretary of the Department of Health, Education and Welfare and charged with the administration of the Act.

4. Defendant Dr. Charles C. Edwards is the Commissioner of Food and Drugs (hereinafter the "Commissioner") and the head of the Food and Drug Administration (hereinafter the "FDA"), a division of the Department of Health, Education and Welfare. He has been delegated by defendant Elliott L. Richardson the authority to administer the Act.

495-151—73——13

5. Ritonic was developed by Ciba for use, under the supervision of a practitioner licensed by law, primarily for persons who are losing their drive, alertness, vitality and zest for living because of the natural degenerative processes of advancing years. It also benefits patients dibilitated or depressed by chronic illness, overwork or recent major surgery.

Ritonic is composed of three types of ingredients. It contains methylphenidate hydrocloride, a central nervous system stimulant which increases alertness and vitality and improves mood and attitude. It also contains male and female hormones which assist the body's capacity to maintain and synthesize protein and otherwise adjust to the decrease in the production of these hormones which occurs with advancing years. The third group of constituents provides a nutritional supplement involving the B-complex of vitamins and the mineral calcium.

6. Ritonic has been marketed commercially since 1959. Its sales volume has averaged approximately 12,000,000 units per year for a total of 134,286,000 units and the yearly gross value of its sales has, in recent years, exceeded $600,000 with a total of $6,456,234 in sales since introduction. With the exception of some limited detailing, ceasing in the second quarter of 1966, these sales have not been assisted by any advertising or other promotional devices since 1961.

7. In July of 1958 Ciba submitted to the FDA a New Drug Application (hereinafter "NDA") for Ritonic. The NDA became effective on January 12, 1959.

8. The NDA was submitted in accordance with § 505 (a) of the Act, 21 U.S.C.A. § 355(a), which at that time and since then has provided that all "new drugs", to be marketed legally, must first have an NDA approved by the FDA.

9. At the time the NDA for Ritonic was submitted, the Act defined a "new drug", 21 U.S.C.A. § 321(p), as any drug not generally recognized as being safe. More particularly the Act provided as follows:

> (p) The term 'new drug' means—
>
> (1) Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof, . . . or

(2) Any drug the composition of which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

10. At the time the NDA for Ritonic was submitted and became effective the Act provided, 21 U.S.C.A. § 355(d), that the Commissioner should deny approval if among other things he found that the application did not include "(1) . . . adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; [or] . . . (3) upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions. . . ."

11. The NDA for Ritonic contained the results of several clinical investigations involving a total of more than 300 patients and indicating that Ritonic was safe and effective for use under the conditions set forth in its labeling. The NDA also cited several articles published in medical journals, based upon clinical studies and attesting to the safety and effectiveness of Ritonic.

Subsequent to the NDA becoming effective Ciba filed reports supplementing the information in the NDA and bringing to the attention of the FDA the results of additional clinical investigations conducted with respect to Ritonic, the reports of adverse reactions to Ritonic which Ciba had received from the field, and the conclusions of additional published articles. At present Ciba is aware of six articles published in medical and scholarly journals which deal specifically with Ritonic and evaluate it on the basis of clinical trials. Each of these articles has concluded that Ritonic is safe and effective.

12. In 1962 the Act was amended, 76 Stat. 780 (hereinafter the "1962 Amendments"), so as to, *inter alia*, allow the Commissioner to withdraw his approval of a New Drug Application effective prior to the amendment if the manufacturer does not demonstrate to the Commissioner not only that the drug is

safe but that there exists "substantial evidence" that the drug will have the effect it purports or is represented to have under the conditions of use recommended in the labeling thereof. 21 U.S.C.A. § 355(e). The Act specifically provides, 21 U.S.C.A. § 355(e), that prior to withdrawal of approval the manufacturer must be accorded an opportunity for a hearing.

13. The term "substantial evidence" is defined in 21 U.S.C.A. § 355(d) to mean

> adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could clearly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof.

14. In July of 1966 the Commissioner contracted with the National Academy of Sciences—National Research Council (hereinafter the "NAS–NRC") for the review by NAS-NRC panels of drugs given NDA approval prior to 1962 to determine whether there exists substantial evidence of the effectiveness of the such drugs for their suggested uses.

15. On September 12, 1969, the Commissioner caused to be published in the Federal Register (Vol. 34, No. 175) a notice (a copy of which is attached hereto as Exhibit A) stating that, based upon the reports received from the NAS–NRC Drug Efficacy Study Group on Ritonic, he had concluded that there was a lack of substantial evidence that Ritonic was effective for the uses recommended or suggested in its labeling and indicating that he intended to initiate proceedings to withdraw approval of the Ritonic NDA. The notice invited Ciba to submit, within 30 days, pertinent data bearing on the proposal to initiate withdrawal proceedings and further stated that the only data which would be considered acceptable would be adequate and well-controlled studies bearing on the efficacy of Ritonic and not previously submitted.

16. Ciba responded to the Commissioner's notice by letter (a copy of which is attached hereto as Exhibit B) dated October 10, 1969, stating its belief that the evidence of the effectiveness of Ritonic previously submitted to the FDA in the NDA

and the annual reports submitted subsequent thereto, including the clinical investigations and published scholarly articles, constituted substantial evidence of the effectiveness of Ritonic. Ciba also reserved the right to assert that Ritonic is not a new drug and therefore not subject to § 505(a) of the Act, 21 U.S.C.A. § 335(a), which requires new drugs to have an approved NDA.

17. On August 5, 1970, the Commissioner caused to be published in the Federal Register (Vol. 35, No. 151) a notice (a copy of which is attached hereto as Exhibit C) stating that he intended to withdraw his approval of the NDA for Ritonic on the ground that there was a lack of substantial evidence that the drug has the effect which it is purported or represented to have under the conditions of use prescribed or recommended in its labeling. The notice further stated that Ciba could request a hearing for the purpose of presenting evidence as to why the NDA approval for Ritonic should not be withdrawn, that such request for a hearing must be accompanied by a full-factual analysis of the clinical and other investigational data Ciba is prepared to prove in support of the effectiveness of Ritonic, and that the hearing would be denied if in the opinion of the Commissioner the request does not present evidence sufficient to create a substantial issue of fact. The notice additionally provided that if the request for a hearing was denied an order would be issued by the Commissioner withdrawing the approval of the NDA for Ritonic and that upon the effectiveness of this order Ritonic would be considered a new drug, the continued marketing of which would render it subject to regulatory proceedings.

18. On August 31, 1970 Ciba replied to the notice of August 5 availing itself of its right to a hearing although reserving its right to maintain that Ritonic is not a new drug in judicial proceedings. (A copy of Ciba's reply is attached as Exhibit D.)

19. Immediately prior to October 1962, Ritonic was "generally recognized . . . as safe" for its labeled uses and had been used to a material extent and for a material time for such uses. Accordingly Ritonic was no longer a "new drug" under the then existing statutory definition set forth in Paragraph 9 hereof.

20. Because Ritonic was not a "new drug" prior to October 10, 1962, it was not covered by an effective NDA. Consequently, any person could have, immediately prior to October 10, 1962, legally commenced or continued the commercial distribution

of Ritonic for its labeled uses, also without having an NDA in effect.

21. The 1962 Amendment to the Act expanded the definition of a "new drug" so as to require that it be generally recognized not only as safe but also as effective. 76 Stat. 780 § 102(a); 21 U.S.C. 321(p). At the time of that amendment, Congress provided that the amendments should not apply to any drug which on the day immediately preceding the enactment of the amendments, October 9, 1962, was (a) commercially used or sold in the United States, (b) was not a new drug as defined by the Act prior to its amendments, and (c) was not covered by an effective NDA. 76 Stat. 780 § 107(c)(4).

22. As a result of the aforesaid exemption any person could lawfully distribute commercially, after October 10, 1962, any drug which that person had commercially distributed prior to that date and which, on that date, was generally recognized as "safe", even though no NDA was in effect for that drug. Ritonic falls within the exemption in view of the fact that on October 9, 1962, it was being commercially sold in the United States, was not a new drug because generally recognized as "safe" and because it was not covered by an effective NDA.

23. Under the notice of opportunity for hearing, the question for consideration at the hearing offered to plaintiff will not be whether or not Ritonic is a new or an old drug because the FDA lacks the power to adjudicate that issue. The hearing will instead be concerned with whether "there is a lack of substantial evidence" of the effectiveness of Ritonic under the conditions of use stated in its labeling. Plaintiff will consequently be unable to present evidence upon the issue that Ritonic is exempt from the Amendments of 1962 by reason of the aforesaid exemption. Accordingly, plaintiff has exhausted all administrative avenues by which it may seek a determination of its rights on this issue.

24. The introduction into interstate commerce of any "new drug" without an effective NDA is prohibited by 21 U.S.C. 331(d) and 505(a) and a violator is subjected to criminal prosecution, 21 U.S.C. 333, injunctive actions, 21 U.S.C. 331 and proceedings leading to the seizure of the defendants' products. 21 U.S.C. 334. Plaintiff would be subject to such proceedings, at the instance of the defendants, if the NDA for Ritonic were withdrawn and, as stated in Paragraph 17 hereof, defendants have threatened such action. In the event of a successful crimi-

nal prosecution the plaintiff could be fined $1,000 and its responsible officers could be subject to such fine or a jail term of one year, or both.

25. Plaintiff's business is dependent upon the confidence of the physicians who prescribe its products and the public which uses them. The institution by the defendants of a criminal, injunctive or seizure action would in and of itself substantially and irreparably affect plaintiff's business because of the reliance by many physicians and the public upon the correctness of such an action by a government agency charged with the regulation of drugs.

26. If Ritonic were withdrawn from the market for even a short period of time Ciba would suffer substantial, immediate and irreparable harm. This harm would arise, *inter alia*, from the fact that the withdrawal of Ritonic from the market would cast a cloud over its reputation which its subsequent re-entry into the market could never suffice to completely remove.

27. The safety of Ritonic is well established and has never been questioned. There will be no threat to the public health if Ritonic continues to be marketed pending the outcome of this action.

28. Plaintiff has no adequate remedy at law.

Wherefore, plaintiff demands judgment as follows:

1. Entering a judgment declaring that Ritonic is exempt from the definition of a new drug by the grandfather exemtion contained in Section 107(c)(4) of the 1962 Amendments to the Act.

2. Permanently enjoining and restraining defendants, and, pending the final determination of this cause, temporarily enjoining and restraining them from attempting to enforce or enforcing against plaintiff the requirements of the Act relating to "new drugs".

3. Such other and further relief as may be appropriate.

SECOND COUNT

1. Plaintiff repeats and makes a part hereof the allegations contained in Paragraphs 1 through 18 of the First Count.

2. As amended in 1962 a new drug is presently defined by the Act, § 201(p), 21 U.S.C.A. § 321(p), as a drug which is not "generally recognized, among experts qualified by scientific training

and experience to evaluate the safety and effectiveness of drugs, as safe and effective under the conditions prescribed, recommended or suggested in the labeling thereof, . . . or . . . any drug [which] . . . has become so recognized but which has not . . . been used to a material extent or for a material time under such conditions."

3. Ritonic is generally recognized among experts qualified by scientific training and experience as safe and effective for use under the conditions recommended in its labeling and has been used to a material extent and for a material time under such ditions.

4. Under the notice of opportunity for hearing, the question for consideration at the hearing offered to plaintiff will not be whether on not Ritonic is a new or an old drug because the FDA lacks the power to adjudicate that issue. The hearing will instead be concerned with whether "there is a lack of substantial evidence" of the effectiveness of Ritonic under the conditions of use stated in its labeling. Plaintiff will consequently be unable to present evidence upon the issue of whether Ritonic is generally recognized as safe and effective. Accordingly, plaintiff has exhausted all administrative avenues by which it may seek a determination of its rights on this issue.

5, Plaintiff repeats and makes a part hereof the allegations contained in paragraphs 24 through 28 of the First Count.

WHEREFORE, plaintiff demands judgment as follows:

1. Entering a judment declaring that Ritonic is not a new drug within the definition of Section 201(p) of the Act as amended, 21 U.S.C. § 321(p), because it is generally recognized as safe and effective.

2. Permanently enjoining and restraining defendants, and, pending the final determination of this cause, temporarily enjoining and restraining them from attempting to enforce or enforcing against plaintiff the requirements of the Act relating to "new drugs."

3. Such other and further relief as may be appropriate.

PITNEY, HARDIN & KIPP,
Attorneys for Plaintiff, Ciba Corporation.
By CLYDE A. SZUCH,
A Member of the Firm.

Dated: September 4, 1970.

31 F.R. 9426 (July 9, 1966)

Food and Drug Administration

NEW DRUGS

Reports of Information for Drug Effectiveness

The National Academy of Sciences-National Research Council (NAS–NRC) has agreed to assist the Food and Drug Administration in its review of the claims of effectiveness for drugs cleared through the new-drug procedures from 1938 until October 10, 1962. To facilitate this review and a determination of whether there may be ground for invoking section 505(e) of the Federal Food, Drug, and Cosmetic Act, and to provide each holder of such an approved new-drug application an opportunity to present for the consideration of the reviewing experts the best data available to support the medical claims, this order is entered pursuant to section 505 of the act:

1. Each holder of a new-drug application approved between 1938 and October 10, 1962, shall report the following, in duplicate, preferably on forms which have been devised by the National Academy of Sciences-National Research Council and which are available for the purpose from the Food and Drug Administration or any of its offices:

a. New-drug application number, date originally approved, and whether Rx or OTC drug.

b. Brand name of drug or preparation.

c. Applicant's (firm's) name and address.

d. Quantitative formula using established (nonproprietary) name of active ingredients.

e. Dosage form and route of administration. Where a new-drug application covers different routes of administration, separate forms should be used.

f. Current labels and package inserts (attach 10 copies of each to original of form; 1 copy of each to duplicate).

g. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, package

insert, or brochure. Approximately 5 to 10 key references, if available (attach 10 copies of the list to original of form and 1 copy to duplicate.

h. Unpublished articles or other data pertinent to an evaluation of the claims (one copy only; attach to duplicate).

2. This report shall be made as promptly as possible and no later than 60 days from the date of this publication in the FEDERAL REGISTER, shall be plainly marked on the outside of the envelope or package "Special Drug Report," and shall be addressed to the Director, Bureau of Medicine (or Director, Bureau of Veterinary Medicine, in the case of veterinary drugs), Food and Drug Administration, Washington, D.C. 20204.

3. The submission of this special report may be made without prejudice to any person's contention that he is not required by law to make the report.

4. This order is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(j), 52 Stat. 1052, as amended, 76 Stat. 732, 21 U.S.C. 355(j)) and under the authority delegated to the Commissioner of Food and Drugs by the Secretary of Health, Education, and Welfare (21 CFR 2.120; 31 F.R. 3003).

Dated: July 6, 1966.

JAMES L. GODDARD,
Commissioner of Food and Drugs.

[F.R. Doc. 66-7489; Filed, July 8, 1966; 8:47 a.m.]

SEPTEMBER 5, 1969.

NDA 11-591 Ritonic ACC 1320

Certified Mail Return Receipt Requested

CIRA PHARMACEUTICAL COMPANY,
556 Morris Avenue,
Summit, New Jersey 07901

GENTLEMEN: Enclosed is the report we have received from the National Academy of Sciences-National Research Council Drug Efficacy Study concerning their evaluation of the claims for your drug product identified above.

An announcement will soon be published in the Federal Register concerning this drug product.

Sincerely yours,

PAUL A. BRYAN, M.D.,
Special Assistant for Drug Efficacy Study Implementation,
Bureau of Medicine.

Enclosure.

National Academy of Sciences—National Research Council—Division of Medical Sciences

DRUG EFFICACY STUDY

FORM A

(To be submitted in duplicate by applicant)

1. NDA Number: 11-591 E-01.
2. Date Originally Approved: 9/3/58.
3. Rx X OTC—.
4. Brand Name: Ritonic.
5. Applicant's Name and Address: CIBA Pharmaceutical Company, 555 Morris Avenue, Summit, New Jersey 07901.
6. Quantitative Formula:

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label):	*Amount (per tablet, per ml., etc.)*
Methylphenidate hydrochloride	5 mg./capsule
Methyltestosterone	1.25 mg./capsule
Ethinyl estradiol	5 meg./capsule
Thiamin	5 mg./capsule
Riboflavin	1 mg./capsule
Pyridoxine hydrochloride	2 mg./capsule
Vitamin B_{12} activity	2 meg./capsule
Nicotinamide	25 mg./capsule
Dicalcium phosphate	250 mg./capsule

7. Dosage form (tablets, etc.): Capsules.
8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.): Oral.
9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).

10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).)
11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.
12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white).

Panel on Psychiatric Drugs

INDICATIONS

I. Ritonic is for patients who are losing their drive, alertness, vitality, and zest for living because of the natural degenerative changes of advancing years

EVALUATION: Ineffective.

COMMENTS: All references supporting the utility of Ritonic itself (as distinct from the Ritalin it contains) are uncontrolled and testimonal although generally positive while focused on aged patient populations. No clear indications for combining these heterogenous ingredients in a single capsule exists.

The Panel considers the combination to be ineffective for this indication, and points out the absence of controlled studies of the individual ingredients vs. the combination, of the individual ingredients vs. each other, and of the combination itself.

DOCUMENTATION:

1. Bachrach, S. A new stimulant supplement for the geriatric patient. J. Amer. Geriat. Soc. 7:408–409, 1959.

2. Bare, W. W. A stimulant for the aged; observations on a methylphenidate-vitamin-hormone combination (ritonic). J. Amer. Geriat. Soc. 8:292–297, 1960.

3. Bare, W. W., and D. Y. P. Lin. A stimulant for the aged; II. Long-term observations with a methylphenidate-vitamin-hormone combination (ritonic). J. Amer. Geriat. Soc. 10:539–544, 1962.

4. George, R. B., and C. H. Lee. A stimulant supplement for the chronically ill: three-month study in a tuberculosis ward. J. Louisiana Med. Soc. 117:239–241, 1965.

5. Natenshon, A. L. Ritonic—a new geriatric supplement. Journal of the American Gariatrics Society 6: 534–538, 1958.

II. Ritonic also benefits patients debilitated or depressed by chronic illness and overwork

EVALUATION: Ineffective.
COMMENTS: Same as for Indication I.
DOCUMENTATION: Same as for Indication I.

III. Ritonic is indicated for patients who are recuperating from illness or surgery

EVALUATION: Ineffective.
COMMENTS: Same as for Indication I.
DOCUMENTATION: Same as for Indication I.
Approved by

_____, *Chairman.*

RITONIC ®

Stimulant and Vitamin-Hormone Supplement

DESCRIPTION

Ritonic is a preparation designed to improve mood and maintain vitality. Each Ritonic capsule contains Ritalin-hydrochloride (methylphenidate hydrochloride (CIBA)—a mild stimulant—and a balanced complement of vitamins, calcium, and hormones. With Ritonic, patients benefit from the mental and physical alerting effects of Ritalin hydrochloride (methylphenidate hydrochloride) as well as anabolic stimulation and nutritional support.

Each Ritonic capsule contains 5 mg methylphenidate hydrochloride, 1.25 mg methyltestosterone, 5 micrograms ethinyl estradiol, 5 mg thiamin (vitamin B_1), 1 mg riboflavin (vitamin B_2), 2 mg pyridoxine hydrochloride (vitamin B_6), 2 micrograms vitamin B_{12} activity (present as cobalamin concentrate), 25 mg nicotinamide, and 250 mg dicalcium phosphate.

Two Ritonic capsules supply ten times the M.D.R.* of vitamin B_1, one and one-half times the M.D.R. of vitamin B_2 and five times the M.D.R. of nicotinamide. The need in human nutrition for vitamin B_6 and B_{12} has not been established.

INDICATIONS

Ritonic is for patients who are losing their drive, alertness, vitality and zest for living because of the natural degenerative changes of advancing years. Ritonic also benefits patients debilitated or depressed by chronic illness, overwork, etc., as well as those recuperating from illness or surgery.

CONTRAINDICATIONS

Marked anxiety, tension, and agitation are contraindications to methylphenidate since the drug may aggravate these symptoms.

Methylphenidate is contraindicated in patients with glaucoma and in patients with epilepsy.

Ethinyl estradiol is contraindicated in females in the presence of breast or genital carcinoma.

Methylestosterone is contraindicated in the presence of carcinoma of the prostate and the breast in males or severe liver damage.

WARNINGS

Ritonic should not be used in patients with severe mental depression.

Because methylphenidate may mask normal fatigue states induced by overexertion, Ritonic should not be used to increase mental or physical capacities beyond physiological limits.

Do not give MAO inhibitors to patients taking Ritonic.

RITONIC

Bare, W.W., *A stimulant for the Aged, Observations on the Methylphenidate-Vitamin-Hormone Combination (Ritonic)*, Journal of the American Geriatrics Society *8* (4): 292–297, April 1960.

Natenshon, A.L., *Ritonic—A New Geriatic Supplement*, Journal of the American Geriatrics Society, *6* (7): 534–538, July 1958.

*Minimal daily requirement.

Bachrach, S., *A New Stimulant Supplement for the Geriatric Patient*, Journal of the American Geriatrics Society, 7 (5): 408–409, May 1959.

George, R.B., and Lee, C.H., *A Stimulant Supplement for the Chronically Ill: Three-Month Study in a Tuberculosis Ward*, Journal of the Louisiana Medical Society, *117* (7): 239–241, July 1965.

Bare, W.W., and Lin, D.Y.P., *A Stimulant for the Aged. II. Long-Term Observations with a Methylphenidate-Vitamin-Hormone Combination* (*Ritonic*) Journal of the American Geriatrics Society, *10* (6): 539–544, June 1963.

Jacobson, A., *The Use of Ritalin in Psychotherapy of Depressions of the Aged*, The Psychiatric Quarterly, p. 1–10, July 1958.

Landman, M.E., Preisig, R., Perlman, M., *A Practical Mood Stimulant*, J. Med. Soc. New Jersey, 55: 1–4, 1958.

Ferguson, J.T., and Funderburk, W.H., *Improving Senile Behavior with Reserpine and Ritalin*, JAMA, 160: 259–263, 1958.

Natenshon, A.L.; *Clinical Evaluation of Ritalin*, Dis. of the Nervous Systems, 17: 392–396, 1956.

34 F.R. 14339 (September 12, 1969)

Food and Drug Administration

Cetylpyridinium Chloride With Benzyl Alcohol Throat Lozenges and Certain Other Drugs

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drugs:

1. Cepacol Throat Lozenges containing cetylpyridinium chloride 1:1500 and 0.3 percent benzyl alcohol; marketed by the Wm. S. Merrell Co., Division of Richardson-Merrell, Inc., 110 Amity Road, Cincinnati, Ohio 45215 (NDA 5-422).

2. Aclor Capsules containing 5 grains glutamic acid hydrochloride per capsule; marketed by Cole Pharmacal

Co., Inc., 3721 Laclede Avenue, St. Louis, Mo. 63108 (NDA 4–484).

3. Flanithin Capsules containing 325 milligrams glutamic acid hydrochloride per capsule; marketed by Table Rock Laboratories, Inc., 812 Hampton Avenue, Greenville, S.C. 29601 (NDA 1–002).

4. Ritonic Capsules containing 5 milligrams methylphenidate hydrochloride, 1.25 milligrams methyltestosterone, 5 micrograms ethinyl estradiol, 5 milligrams thiamine mononitrate, 1 milligram riboflavin, 2 milligrams pyridoxine hydrochloride, 2 micrograms cobalamin concentrate, 25 milligrams niacinamide, and 250 milligrams dibasic calcium phosphate per capsule; marketed by Ciba Pharmaceutical Co., 556 Morris Avenue, Summit, N.J. 07901 (NDA 11–591).

5. Am Plus Improved Capsules containing per capsule 5 milligrams dextroamphetamine sulfate, 5 milligrams hydroxyzine hydrochloride, and Vitamin A palmitate, ergocalciferol, thiamine mononitrate, riboflavin, pyridoxine hydrochloride, niacinamide, sodium ascorbate, ascorbic acid, calcium pantothenate, cobalamin concentrate, dibasic calcium phosphate, cobaltous sulfate, cupric sulfate, potassium iodide, ferrous fumarate, manganous sulfate, sodium molybdate, magnesium sulfate, potassium sulfate and zinc sulfate; marketed by J. B. Roerig & Co., Division, Chas. Pfizer & Co., Inc., 235 East 42d Street, New York, N.Y. 10017 (NDA 11–852).

6. Liquid Germicidal Detergent containing 2½ percent benzethonium chloride; marketed by Parke, Davis and Co., Joseph Campau at the River. Detroit, Mich. 48232 (NDA 5–616).

7. Phemerol Tincture containing benzethonium chloride 1:500, and alcohol 65 percent; marketed by Parke, Davis and Co. (NDA 4–232).

8. Phemerol Solution containing benzethonium chloride 1:750; marketed by Parke, Davis and Co. (NDA 4–231).

9. Phemerol Topical containing 3 percent benzethonium chloride; marketed by Parke, Davis and Co. (NDA 5-113).

10. Bilcain Tablets containing 3 grains ox bile extract, ⅛ grain aloin, and ½ grain cascara sagrada extract per tablet; marketed by Cole Pharmacal Co., (NDA 3–420).

11. Ethylene Disulphonate (Allergosil Brand) Ampoules containing ethylene disulfonate in a dilution of 10^{-15} sterile water for injection; marketed by Spicer-Gerhart Co., 23 North Sycamore, Pasadena, Calif. 91107 (NDA 5–127).

12. Alertonic Elixir containing in each 45 cubic centimeters: 2 milligrams pipradrol hydrochloride, 10 milligrams thiamine hydrochloride, 5 milligrams riboflavin, 1 milligram pyridoxine hydrochloride, 50 milligrams niacinamide, 100 milligrams choline chloride, 100 milligrams inositol, 100 milligrams calcium glycerophosphate, 1 milligram manganous sulfate, 1 milligram magnesium acetate, 1 milligram zinc acetate, 1 milligram ammonium molybdate, and alcohol; marketed by The Wm. S. Merrell Co. (NDA 10–740).

The Food and Drug Administration has concluded that there is a lack of substantial evidence that these drugs are effective for all the uses recommended or suggested in their labeling and that each component of the combination drugs contributes to the total effects claimed for such drugs.

The Commissioner of Food and Drugs intends to initiate proceedings to withdraw approval of the new drug applications for these drugs. Prior to initiating such action, however, the Commissioner invites the holders of new drug applications for these drugs, and any interested person who may be adversely affected by removal of these drugs from the market, to submit any pertinent data bearing on the proposal within 30 days following the date of publication of this notice in the FEDERAL REGISTER. The only material which will be considered acceptable for review must be well-organized, and consist of adequate and well-controlled studies bearing on the efficacy of the products and not previously submitted.

This announcement of the proposed action and implementation of the NAS–NRC report for the above drugs is made to give notice to persons who might be adversely affected by withdrawal of these drugs from the market. Promulgation of an order withdrawing approval of the new drug applications will cause any such drug on the market offered for these uses, to be a new drug for which an approved new drug application is not in effect, and will make it subject to regulatory action.

495-151—73——14

A copy of the NAS–NRC report has been furnished to each firm referred to above. Any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be identified with the reference number, DESI 1002, and should be directed to the attention of the following appropriate office and addressed to the Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204.

Request for NAS–NRC report: Press Relations Office (CE–300).

All other communications regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (MD–16), Bureau of Medicine.

This notice is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended, 21 U.S.C. 352, 355) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: September 4, 1969.

HERBERT L. LEY, Jr.,
Commissioner of Food and Drugs.

[F.R. Doc. 69–10875; Filed, Sept. 11, 1969; 8:45 a.m.]

OCTOBER 10, 1969.

NDA 11–591 Ritonic
Re: DESI 1002.

SPECIAL ASSISTANT FOR DRUG EFFICACY
STUDY IMPLEMENTATION,
Bureau of Medicine (MD–16),
Food and Drug Administration,
200 C Street, S.W.,
Washington, D.C. 20204.

GENTLEMEN: The Federal Register of September 12, 1969, (Vol. 34, No. 175) contained a notice that the Commissioner of Food and Drugs intends to initiate proceedings to withdraw approval of the new application for Ritonic, No. 11–591.

CIBA wishes to advise you that it does not agree with the conclusions set forth in that notice that there is a lack of substantial evidence that Ritonic is effective for the uses recommended or suggested in its labeling and that each component of

the combination contributes to the total effect claimed for the drug.

The September 12, 1969, notice provided for the submission within a thirty-day period of pertinent data "not . . . previously submitted". In addition to the material submitted by CIBA in the "Special Drug Report" for Ritonic filed in response to the Federal Register notice dated July 9, 1966, (Vol. 31, No. 132), we submit herewith, by incorporation by reference, the data and material heretofore submitted and referred to in the Ritonic New Drug Application, in supplements thereto, and in periodic and in all other reports filed by CIBA with the Food and Drug Administration with regard to Ritonic.

CIBA reserves all rights to assert that Ritonic is not a new drug and is not subject to the provisions of Section 505 of the Food, Drug and Cosmetic Act as amended (21 U.S.C. 355).

We wish to advise you that should the Commissioner initiate proceedings to withdraw approval of the new drug application for Ritonic, we reserve our right to avail ourselves of the opportunity for hearing provided for in Section 505 of the Food, Drug and Cosmetic Act (21 U.S.C. 355).

Sincerely yours,

CIBA PHARMACEUTICAL COMPANY,
JOSEPH S. HARUN, M.D.,
Executive Director,
Drug Regulatory Affairs Division.

35 F.R. 12495 (August 5, 1970)

Food and Drug Administration

[Docket No. FDC–D–207: NDA No. 11–591]

CIBA PHARMACEUTICAL CO.

Ritonic Capsules; Notice of Opportunity for Hearing on Proposal To Withdraw Approval of New-Drug Application

In an announcement (DESI 1002) published in the FEDERAL REGISTER of September 12, 1969 (34 F.R. 14339), CIBA Pharmaceutical Co., 556 Morris Avenue, Summit, N.J. 07901, the holder of new-drug application No. 11–591 for Ritonic Capsules containing 5 milligrams methylphenidate hydrochloride, 1.25

milligrams methyltestosterone, 5 micrograms ethinyl estradiol, 5 milligrams thiamine mononitrate, 1 milligram riboflavin, 2 milligrams pyndoxine hydrochloride, 2 micrograms cobalamin concentrate, 25 milligrams niacinamide, and 250 milligrams dibasic calcium phosphate per capsule, as well as any other interested person, were invited to submit pertinent data bearing on the intention of the Commissioner of Food and Drugs to initiate proceedings to withdraw approval of the new-drug application.

CIBA responded to the announcement: however, the information submitted does not provide substantial evidence of effectiveness of the drug for its recommended uses, that is: In patients who are losing their drive, alertness, vitality and zest for living because of the natural degenerative changes of advancing years; patients debiliated or depressed by chronic illness or overwork: and patients who are recuperating from illness or surgery.

Therefore, notice is given to CIBA Pharmaceutical Co. and to any other interested person who may be adversely affected that the Commissioner proposes to issue and order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(c)) withdrawing approval of new-drug application No. 11–591 and all amendments and supplements thereto for Ritonic Capsules on the grounds that new information before the Commissioner with respect to such drug, evaluated with the evidence available to him when the application was approved, shows there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the applicant, and any interested person who would be adversely affected by an order withdrawing such approval, an opportunity for a hearing to show why approval of the new-drug application should not be withdrawn. Promulgation of the proposed order will cause any drug for human use containing the same components and offered for the same conditions of use to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

Within 30 days after publication hereof in the FEDERAL REGISTER, such persons are required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6–62, 5600 Fishers Lane, Rockville, Md. 20852, a written appearance electing whether:

1. To avail themselves of the opportunity for a hearing; or

2. Not to avail themselves of the opportunity for a hearing.

If such persons elect not to avail themselves of the opportunity for a hearing, the Commissioner without further notice will enter a final order withdrawing approval of the new-drug application. Failure of such persons to file a written appearance of election within said 30 days will be construed as an election by such persons not to avail themselves of the opportunity for a hearing.

The hearing contemplated by this notice will be open to the public except that any portion of the hearing that concerns a method or process the Commissioner finds entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance.

If such persons elect to avail themselves of the opportunity for a hearing, they must file within 30 days after the publication of this notice in the FEDERAL REGISTER a written appearance requesting the hearing, giving the reasons why approval of the new-drug application should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data they are prepared to prove in support of their opposition to this notice. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that a genuine and substantial issue of fact requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that no genuine and substantial issue of fact preclude, the withdrawal of approval of the application, the Commissioner will enter an order on these data, making findings and conclusions on such data.

If a hearing is requested and is justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence, not more than 90 days after

the expiration of such 30 days unless the hearing examiner and the person(s) requesting the hearing otherwise agree (35 F.R. 7250, May 8, 1970).

This notice is issued pursuant to provisions of the Federal Food, Drug and Cosmetic Act (sec. 505, 52 Stat. 1052–53, as amended; 21 U.S.C. 355) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: July 24, 1970.

SAM D. FINE,

Acting Associate Commissioner for Compliance.

[F.R. Doc. 70-10145, Filed, Aug. 4, 1970; 8:48 a.m.]

AUGUST 31, 1970.

NDA 11–591, Ritonic Capsules

HEARING CLERK,
Department of Health, Education, and Welfare,
Room 6–62, 5600 Fishers Lane,
Rockville, Maryland 20852

DEAR SIR: CIBA Pharmaceutical Company, a Division of CIBA Corporation, hereby makes a written appearance in response to the Notice of Opportunity for Hearing on Proposal to Withdraw Approval of New Drug Application No. 11-591 (Ritonic Capsules) published in the Federal Register of August 5, 1970.

As provided for in Section 505(e) of the Food, Drug and Cosmetic Act (21 U.S.C. 355) CIBA hereby elects to avail itself of the opportunity for a hearing.

The August 5, 1970, Notice of Opportunity for Hearing requires the applicant electing to avail itself of the opportunity to state the reasons why approval of the New Drug Application should not be withdrawn. For the reasons set forth in the complaint filed by the Pharmaceutical Manufacturers Association in the United States District Court for the District of Delaware on July 23, 1970, this is an improper demand.

We wish to advise you that it is CIBA's position that Ritonic Capsules are not now a new drug under the Food, Drug and Cosmetic Act, as amended and that the amendments of 1962 are not applicable to that drug. Therefore, this election to avail ourselves of the opportunity for a Hearing is made with

a reservation of the right to establish these facts in the administrative proceedings, or in judicial proceedings, or both.

Sincerely yours,

JOSEPH S. HARUN, M.D.,
Executive Director,
Drug Regulatory Affairs Division.

JSH:lar

35 F.R. 15253 (September 30, 1970)

Food and Drug Administration

[Docket No. FDC-D-207; NDA No. 11-591]

CIBA PHARMACEUTICAL CO.

Ritonic Capsules; Notice of Withdrawal of Approval of New-Drug Application

On August 5, 1970, there was published in the Federal Register, 35 F.R. 12495. A notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new-drug application No. 11-591 for Ritonic Capsules and all amendments and supplements thereto on the ground that there is a lack of substantial evidence that Ritonic Capsules have the effect they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.

CIBA Pharmaceutical Co., a division of CIBA Corp., Summit, N.J. 07901, holder of NDA No. 11-591 for Ritonic Capsules, filed a letter requesting a hearing pursuant to the August 5, 1970 publication, but did not file any data to support such request and provided no reasons why approval of NDA No. 11-591 should not be withdrawn, as required by the August 5, 1970, publication. The Commissioner of Food and Drugs concludes there are no genuine substantial issues of fact to justify a hearing (35 F.R. 7250; May 8, 1970).

The Commissioner of Food and Drugs, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (Section 505(e), 52 Stat. 1052, as amended; 21 U.S.C. 355(e)) and under authority delegated to him (21 CFR 2.120), finds that on the

basis of new information before him with respect to said drug, evaluated together with the evidence available to him when the application was approved, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Therefore, pursuant to the foregoing finding, approval of the above new-drug application, and all amendments and supplements thereto, is withdrawn effective on the date of the signature of this document.

Dated: September 21, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70-12989; Filed, Sept. 29, 1970; 8:46 a.m.]

EXCERPTS FROM TRANSCRIPT OF PROCEEDINGS IN DISTRICT COURT, JANUARY 11, 1971

[23] [Mr. SZUCH.] * * *

All of the correspondence from the Commission to my client, Ciba, has been: "Present evidence on safety and efficacy." The invitation to submit and the invitation to participate in the hearings obviously stem from a conclusion formed by the Commission that they have a new drug. Therefore, under the statute you must establish safety and efficacy.

The COURT. Suppose the Court of Appeals reverses the determination? Reverses the determination of the Commissioner below? You would be all right then. You would get a——

Mr. SZUCH. I have nothing in the record before the Court of Appeals on the issue at all, your Honor.

The COURT. The Court of Appeals is either going to affirm or reverse or remand.

Mr. SZUCH. Based on the record from the Court of Appeals, on this issue it would have to affirm.

Neither side has anything in the record, I don't believe—Counsel for the government and I have not seen the record and I don't believe that Ciba has submitted any information which would constitute part of this record relating to the issue of general recognition of safety and efficacy, and we can ask the government's attorney right now if the government has.

Mr. ANDERSON. Ciba has submitted a nine-item bibliography which referenced part of which was in the medical [24] literature together with a fifty-page 690-item bibliography concerning all of the constituents of the drugs which cite references to the world medical literature concerning the safety and efficacy of Ritonic capsules. This bibliography, together with the available reprints, is in the record.

Mr. SZUCH. That information is submitted on the issue of safety and efficacy, but there is no evidence in the record of general recognition of safety and efficacy which is a fair different issue from the issue which is now before the Court of Appeals or that may be before the Court of Appeals, if this Court decides that it doesn't have jurisdiction.

The COURT. While that case is pending in the Court of Appeals for the Second Circuit, is the government doing anything to Ciba? Is it seizing the drug?

Mr. SZUCH. No, it is not.

The COURT. Does it intend to before that Court decides the issue?

Mr. SZUCH. The government and we have entered into an agreement, your Honor, on an informal basis, that no action will be taken without giving us prior notice to that effect pending the resolution of the matter and we would expect, your Honor, as I indicated, as far as the Second Circuit decision is concerned, or as far as the appeal is concerned, depending on your Honor's ruling. If your Honor rules that you have jurisdiction here which we think you do, [25] we will immediately dismiss the Court of Appeals action because we don't think that you can or should go both ways.

If we are correct in the position that we have advanced before your Honor, our notice of appeal in the Court of Appeals is properly dismissable on motion.

Mr. ANDERSON. If I may, your Honor, I would just like to—and, again, I don't wish to engage in any extended colloquy with counsel on this now—but, for the record, counsel did mention it. The nature of whatever informal agreement may have been made between Mr. Szuch and myself is not quite as he puts it. At the time that the T.R.O. was in question and there was a point in time when Ciba was going to come before you on T.R.O., we did informally work out an agreement whereby at that time no action would be taken with respect to this drug until Ciba had been contacted again and fully apprised of the

agency's position. I think now, your Honor, that has been achieved, and I should point out to your Honor that in this regard that the statute provides—by "the statute" I refer to Section 505(h)—that a stay is available from the Court of Appeals on the application of the——

The COURT. Do you think that the government will voluntarily agree to a stay pending the decision of the Court of Appeals?

Mr. ANDERSON. I am not prepared to answer that question [26] your Honor, until the application is made to the Court of Appeals for such a stay and it was made by the Ciba Corporation. They made no such application.

The COURT. I understand. Mr. Szuch says that he is not interested in my Court—if I take it on.

Mr. ANDERSON. Your Honor, if I may, I have no comment on the on-again off-again approach to the separate service, but I believe that here for our purposes it simply will not wash to say that a statute which grants authority to the Court of Appeals to review a final order on the question which resolves all available evidence on the safety and efficacy of a particular drug and whether or not it is generally recognized by the experts well qualified in their field as safe and effective, somehow withhold authority from the Court of Appeals to determine the fundamental question of whether or not the drug involved is a new drug. That is, whether it is generally recognized as safe and effective. The petitioners—the plaintiff—has cited no case for that proposition. To the contrary, and as your Honor pointed out, the expertise as a matter of primary jurisdiction, is very important and has been judicially recognized and preserved in a variety of cases which we have cited to your Honor. More particularly, although, of course, not binding on your Honor, the propriety of raising the not-a-new-drug issue and the grandfather issue at the agency level for later review by the [27] Court of Appeals has been expressly recognized by Judge Northrup in Hinson Westcott v. Dunning, down in Delaware.

The COURT. You will agree with me that under the declaratory judgment that it would be discretionary whether or not I entertain this application?

Mr. ANDERSON. Your Honor, it is in any event within your Honor's discretion to issue the relief sought, and I think regardless of the cases cited, no factual case here has been made out which would authorize or warrant your Honor's assertion of

your discretionary jurisdiction to grant the relief that the plaintiff seeks.

The COURT. Well, you are asking for two things, and we know we are not talking about the merits. We eliminated that. You are talking only about jurisdiction now.

Mr. ANDERSON. That is correct, and we are asking now that the action be dismissed.

The COURT. Mr. Szuch, what about that? It could be if I had jurisdiction. Under the Declaratory Judgment Act I could in the exercise of a sound discretion say to you, "I am sorry, I will not entertain the action here because you have got one pending in the Court of Appeals for the Second Circuit."

Now, it would seem to me, and I have given this a lot of thought, that because of the nature of the application this is new law, really. A lot of these cases just recently [28] coming down, and some of them—You can see that some of them have not been clearly thought out, but that is neither here nor there. I feel that under all of the circumstances that even assuming that I do have jurisdiction to determine the question that you put to me, that in the exercise of my discretion I would decline and refuse to exercise that jurisdiction and grant the government's motion, and leave you to pursue your remedy in the Court of Appeals.

Mr. SZUCH. Your Honor, in order to reach that result I think your Honor would also have to reach the conclusion, contrary to what we have put forward, that we have an adequate remedy in the Court of Appeals. We would submit to your Honor that we do not. The issue that we would expect to move before your Honor of general recognition of safety and effectiveness is one which we do not believe is before the Court of Appeals.

The COURT. Is before the Court of Appeals.

Mr. SZUCH. We have not produced a record of that issue before the Commission. We have no record on that before the Court of Appeals. Indeed, if we would expect that that issue is to be adjudicated, that many experts would have to be gotten, and we would have to take the depositions of some of the experts of the government on whom they intend to rely and there is a great factual investigation and presentation which must be made to some trier of the facts, and I don't really believe that the [29] Court of Appeals is going to sit as a trial Court or should sit as a trial Court on that issue. They are a reviewing Court to review the propriety or impropriety of the Commissioner's action.

The COURT. I agree with that. That is what it is doing, but how would you be hurt if you had this issue, whatever it may be, or as narrow as you want to construe it to be, that is now pending before the Court of Appeals? How would you be hurt if the matter is left there with a stay application that the——

Mr. SZUCH. Let us assume that the Court of Appeals resolves the issue and affirms the Commissioner without getting to the issue that I am trying to try before your Honor which I submit is very possible on the record going to the Court of Appeals. We would then be faced with a seizure.

The COURT. And then this Court would be available.

Mr. SZUCH. That is correct, which then means that we will have to subject the Ciba Corporation to possible criminal action.

The COURT. If they seize you, you come in to see me at any time. Then we have cases which clearly indicate that the District Court has jurisdiction. When there has been a seizure.

Mr. SZUCH. That is correct, your Honor, but may I suggest that if your Honor concludes you have jurisdiction [30] when there is a seizure, why would there be anything different for declaratory judgment relief? There is nothing peculiar or different about an action for a declaratory judgment. We have got to find initial jurisdiction. It is peculiar in a sense that you must exercise your discretion, but other than that whether it be a declaratory judgment or a suit as of right, such as a seizure action, we must first posit the action on the Court having jurisdiction.

The COURT. I have jurisdiction in a seizure case. What do I decide in a seizure case? Whether the seizure was right or wrong.

Mr. SZUCH. And in that connection, your Honor——

The COURT. This is much narrower then.

Mr. SZUCH. No, it won't be, because in order to decide whether the seizure was right or wrong the defense which would be raised possibly, and I don't know what the effect of the Court of Appeals opinion would be, but let's assume it does not bar me collaterally, the issue at the time will be whether the defense that this is not a new drug and therefore no N.D.A. must be in effect will be raised. Your Honor will then have to decide in face whether Ritonic is a new or old drug. On that issue, your Honor, you will have to determine

whether there is general recognition of safety and efficacy, the exact issue which I am suggesting to your Honor to decide now. Now, if you [31] are prepared to say that you would be in a position jurisdition-wise to decide it in a seizure action, then I would suggest to your Honor that other than the discretion portion, which I will pass for the moment, the question of jurisdiction remains the same as the declaratory judgment entry.

The COURT. I get your argument. What do you have to say?

Mr. ANDERSON. In response to that last point, your Honor, I have only this to say: Mr. Szuch asks rhetorically what is the difference between a seizure action as this action now. The answer is, in the posture of this case, that we are at the end of a lengthy administrative process which Congress has mandated for the review of new drug applications. Congress said, "First you go to the agency and you have your hearing and you establish your record and then you go to the Court of Appeals and you review the record." In the posture of seizure cases, however, there is no new drug application involved. We are at the outset of the matter, the agency has encountered a substance on the market, has determined that the claims made for it are not justified by general recognition of safety and efficacy and has moved by motion for an order of the Court to detain the article. A totally different regulatory posture, your Honor, not at all like what is here.

[32] As your Honor has indicated in that situation, clearly you have jurisdiction. Clearly, you have not only the opportunity but the obligation to determine whether or not the agency has proceeded properly. This is not the case now.

The COURT. Don't you think that I might have jurisdiction in this case, under the Declaratory Judgment Act?

Mr. ANDERSON. I am not prepared to say that you do, your Honor, in the face of those Courts which have spoken on the issue.

Your Honor is right that this is new law, and the decisions are only now coming down, as evidenced by our brief. I can only tell you that what Judge Fulham has told us in Lemon, and what Judge Northrup has told us in Hinson, Westcott and Dunning is that these issues are properly raised before the agency, for review by the Court of Appeals. They recognize the lack of facilities and the lack of necessity for the District Court

to intervene and hold a separate trial on the issue, observing that there was available perfectly adequate review in the Court of Appeals on all legal and factual issues. So to that extent, based on what has been said by the District Court, I think that your Honor does not have justification for asserting what is discretionary jurisdiction.

The COURT. Well, I am going to decide this by granting the defendant's motion for dismissal of the action. I [33] do not think in the present posture of this case that I do have jurisdiction, but even assuming that I did have jurisdiction under the Declaratory Judgment Act I would exercise my discretion and dismiss the action.

That will be the decision of the Court. There will be no costs allowed. Submit an appropriate order, and then, Mr. Szuch, that will give you an opportunity to take the train and go to Philadelphia.

United States District Court for the District of New Jersey

[Caption omitted]

ORDER

This matter being opened to the Court by Frederick B. Lacey, United States Attorney for the District of New Jersey (Richard M. Langway, Assistant U.S. Attorney and Robert N. Anderson, Esq. appearing) in the presence of Pitney, Hardin & Kipp, attorneys for plaintiff (Clyde A. Szuch, Esq. appearing) on a motion of defendants for an order of dismissal for lack of jurisdiction of the subject matter or in the alternative for summary judgment of dismissal; and the Court having considered the pleadings and memoranda of law filed in support of and in opposition to the motion; and the Court having heard and considered the arguments of counsel and having rendered its decision in open court on January 11, 1971; and good cause having been shown

IT IS ON THIS 10th DAY OF MARCH, 1971

ORDERED that defendants' motion for dismissal of the complaint for lack of jurisdiction over the subject matter be and the same is hereby granted and the complaint is dismissed, without costs.

ANTHONY T. AUGELLI, U.S.D.J.

United States Court of Appeals For the Third Circuit

No. 71–1512

CIBA CORPORATION, A CORPORATION OF THE STATE OF DELAWARE, APPELLANT

vs.

ELLIOTT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION & WELFARE AND DR. CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

Appeal From the United States District Court for the District of New Jersey

Argued April 11, 1972

Before HASTIE, VAN DUSEN and ALDISERT, *Circuit Judges*

OPINION OF THE COURT

[Filed June 5, 1972]

PER CURIAM:

Ciba Corporation has taken this appeal from an order of the District Court for the District of New Jersey dismissing a complaint in which Ciba sought a declaratory determination that its drug product, Ritonic Capsules, is exempt from the requirement of 1962 amendments of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355, that new drugs be excluded from the market unless proven effective as claimed for them. The complaint also sought an injunction against the implementation of an administrative order, entered by the Commissioner of Food and Drugs after notice and opportunity for an evidentiary hearing, that withdrew approval of the drug upon the basis of a finding that the manufacturer's claims as to its effectiveness were unproven. On appeal, the Court of Appeals for the Second Circuit has affirmed that order. *Ciba-Geigy Corp.* v. *Richardson*,

1971, 446 F.2d 466. That affirmance occurred after the district court had dismissed the present suit and is subject to review by the Supreme Court.

The appellant's basic position seems to be that neither the Commissioner in an administrative proceeding under § 355(e) to determine whether lack of effectiveness as claimed makes a drug unmarketable, nor a court of appeals in reviewing the administrative decision, has jurisdiction to decide as to threshold question whether the product in controversy is a "new drug" within the meaning of the statute, § 355, that covers "new drug" applications and administrative proceedings pursuant thereto. We find no merit in that argument. Inherent in the grant of administrative competency to conduct and decide new drug proceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such a proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision.

In disapproving Ritonic Capsules the Commissioner and the Court of Appeals for the Second Circuit necessarily decided that the 1962 amendments of the Act were applicable to that product. That determination is reviewable by the Supreme Court. It is neither necessary nor appropriate that the District Court for the District of New Jersey entertain a separate suit by the loser in the administrative proceedings and in the direct appeal therefrom for a redetermination of the same question.

The judgment will be affirmed.

In the United States Court of Appeals for the Third Circuit

No. 71–1512

CIBA CORPORATION, APPELLANT,

vs.

ELLIOTT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION & WELFARE AND DR. CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS.



(D. C. Civil Action No. 1210–70)

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY

Present: HASTIE, VAN DUSEN and ALDISERT, *Circuit Judges.*

JUDGMENT

This cause came on to be heard on the record from the United States District Court for the District of New Jersey and was argued by counsel.

On consideration whereof, it is now here ordered and adjudged by this Court that the judgment of the said District Court, filed March 10, 1971, be, and the same is hereby affirmed, with costs taxed against appellant.

Attest:

(S) THOMAS F. QUINN, *Clerk.*

June 5, 1972

Certified as a true copy and issued in lieu of a formal mandate on June 27, 1972.

Test:

(S) THOMAS F. QUINN
Clerk, United States Court of Appeals For The Third Circuit.

In the Supreme Court of the United States

No. 72–528

CIBA CORPORATION, PETITIONER,

v.

ELLIOTT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE, ET AL.

ORDER ALLOWING CERTIORARI. FILED JANUARY 8, 1973

The petition herein for a writ of certiorari to the United States Court of Appeals for the Third Circuit is granted. The case is consolidated with Nos. 72–394, 72–414, 72–555 and 72–666, and a total of three hours is allotted for oral argument.

United States Court of Appeals for the Fourth Circuit

(Civil No. 71–1243)

BENTEX PHARMACEUTICALS, INC., ET AL., APPELLANTS

v.

ELLIOT L. RICHARDSON, ET AL., APPELLEES

RELEVANT DOCKET ENTRIES

Date	
3/11/71	Record on appeal in one volume (Volume I) filed and appeal docketed.
3/11/71	Exhibits in one envelope received from the Clerk of the District Court at Columbia, South Carolina.
3/16/71	Appearance for the appellants filed and entered.
3/19/71	Appellants' designation of the portions of the record to be included in the appendix and statement of issue filed.
4/15/71	Appearance for the appellees filed and entered.
4/20/71	Brief for appellants filed. 25 copies.
5/19/71	Appellee's motion for enlargement of time to file its brief to June 30, 1971, filed. Motion granted.
7/ 6/71	Brief and appendix for appellees filed. 25 copies.
7/ 8/71	Appellants' motion for enlargement of time to file reply brief to July 31, 1971, filed. Motion granted.
7/26/71	Motion for enlargement of time to file appellant's reply brief to 8–15–71 filed. Motion granted.
8/13/71	Reply brief for appellants filed. 25 copies.
11/16/71	Notice of oral argument mailed to Townes, Abrams, Epstein, Goodrich, and Anderson.
12/ 8/71	Appearance for appellee filed and entered.
12/ 8/71	Cause argued before Winter, Russell and Field, Circuit Judges, and submitted.
12/17/71	Above record on appeal with tape mailed to Judge Russell.

Date	
5/12/72	Record on appeal in one volume and exhibits in one envelope received from Judge Russell.
5/23/72	Opinion filed.
5/23/72	Opinion and Clerk's Memorandum mailed to counsel of record. (Mailed to Townes, Abrams and Epstein.) Copy of opinion mailed to the Clerk of the District Court at Greenville, South Carolina.
5/23/72	Judgment of the district court remanded with directions. Judgment filed.
6/14/72	Certified copy of the judgment and printed copy of the opinion transmitted to the Clerk of the District Court at Columbia, S.C.
6/14/72	Record on appeal in one volume and exhibits in one envelope returned to the Clerk of the District Court at Columbia, S.C.
10/10/72	Notice evidencing the filing petition for certiorari in the Supreme Court October 5, 1972 filed. (No. 72–555)
1/12/73	Order of the Supreme Court granting certiorari January 8, 1973 filed.
2/ 2/73	Record on appeal in one volume and exhibits in one envelope received from the Clerk of the District Court at Columbia, South Carolina.
2/ 2/73	Certified record in two volumes and exhibits in one envelope transmitted to the Clerk of the Supreme Court.

In the United States District Court for the District of South Carolina

GREENVILLE DIVISION

(Complaint C/A No. 70–1001)

O'NEAL, JONES & FELDMAN, INC., BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMACEUTICAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC., SOUTHERN DRUG & MFG. CO., THE

BLAINE COMPANY, BROWN PHARMACEUTICAL CO., MAYRAND, INC., PHARMACEUTICAL ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHARMACEUTICALS, INC., BCR PHARMACAL CO., INC., ALTO PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES, INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMACEUTICAL PRODUCTS, INC., FOS PHARMACEUTICAL CO., W. E. BOODY & CO., PLAINTIFFS

vs.

ELLIOT P. RICHARDSON, SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, DEFENDANTS.

The plaintiffs, complaining of the defendants, would respectfully show the Court:

I.

The Food and Drug Administration is an agency of the United States of America under the Department of Health, Education and Welfare. Elliot P. Richardson is the Secretary of the Department of Health, Education and Welfare, and Charles C. Edwards is the Commissioner of the Food and Drug Administration, and they are made parties to this action in their said representative capacities.

II.

One of the plaintiffs, Pisgah Pharmaceuticals, Inc., is a South Carolina Corporation, having its principal place of business in Greenville, South Carolina, a place within the physical jurisdiction of this Court.

III.

The plaintiffs are corporations a part of whose business involves the manufacture and/or sale and distribution of drugs in interstate commerce containing pentylenetetrazol and/or nicotinic acid; except the plaintiff, O'Neal, Jones & Feldman, Inc., and that plaintiff contemplates engaging in said business.

IV.

The sale of these several drugs in interstate commerce is regulated by Title 21, Chapter 9 of the United States Code, called the Federal Food, Drug and Cosmetic Act.

V.

The Food and Drug Administration is granted and charged with the exercise of administrative and regulatory powers and duties under said act.

VI.

This action is brought under Title 5, Chapter 7 of the United States Code.

VII.

The Food and Drug Administration published in the FEDERAL REGISTER, Vol. 35, No. 98, dated Wednesday, May 20, 1970, on page 7749 a notice entitled "Pentylenetetrazol-Containing Drugs." The contents of the notice are fully set forth in Exhibit A of this complaint, and contents of said exhibit are incorporated by reference as part of the allegations of this paragraph.

VIII.

This notice was issued in proceedings instituted for the withdrawal of approval of new-drug applications for Geroniazol Injection (NDA 11–742) and Nicozol with Reserpine tablets (NDA 10–508), containing the ingredients and proportions as set forth in said notice. These new-drug applications were held by Phillips Roxane Laboratories, Division of Phillips Roxane, Inc. and Nysco Laboratories, Inc. Hart Laboratories, holder of NDA 11–347, Nicozol with Reserpine Tablets, was a party to said proceedings.

IX.

The proposed order of which notice was given was to the effect that approval of the above new-drug applications would be withdrawn "on the grounds that there is a lack of substantial evidence that these drugs have the effect they purport to have under the conditions of use prescribed, recommended, or suggested in their labeling."

X.

The said notice contained this language:

> Promulgation of the purposed order will cause any drug for human use containing the same active sub-

stances to be a new drug for which an approved new drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

XI.

The orders proposed by the notice were issued on September 3, 1970 at CFR 2:120. Said orders are fully set forth as Exhibit B of this complaint and the contents of said exhibit are incorporated by reference as part of the allegations of this paragraph.

XII.

The plaintiffs are informed and believe that the Food and Drug Administration contemplates and is about to institute such regulatory proceedings against the plaintiffs.

XIII.

Title 21, Section 321 (p) (1) United States Code, defines the term "new drug" as follows:

> (p) The term 'new drug' means—(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that it is not generally recognized, among experts qualified by the scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed a 'new drug' if at any time prior to the enactment of this chapter it was subject to the Food and Drug Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use. . . .

XIV.

The drugs, pentylenetetrazol and nicotinic acid, were subject to the Food and Drug Act of June 30, 1906, as amended, prior to the enactment of said chapter.

XV.

The enactment of said chapter was October 9, 1962.

XVI.

The manufacture and distribution of said drugs in interstate commerce by the plaintiffs has been under the exception (called the "grandfather clause") provided for in Title 21, Section 321 (p) (1) as quoted above, and/or under the claim that said drugs are not "new drugs" as therein defined, and not under any new-drug application.

XVII.

None of the plaintiffs was a party to the proceedings resulting in the notice and orders contained in Exhibits A and B of this complaint.

XVIII.

The plaintiffs are informed and believe that the provisions of the notice alleged in Paragraph X, and the policy, intention, and decision of the Food and Drug Administration as therein enunciated, are invalid and nugatory for the reasons alleged herein:

(1) The declaration that any drug on the market containing the "same active substances" is a "new drug" cannot lawfully be made in a proceeding brought for the withdrawal of approval of one or more specified new-drug applications under Section 355, Title 21.

(2) Said declaration cannot lawfully be made on the basis that there is "a lack of substantial evidence that these drugs have the effect they purport to have under the conditions of use prescribed, recommended, or suggested in their labeling", but only on the basis that such drugs are "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for the use under the conditions prescribed, recommended, or suggested in the labeling thereof . . .", the latter being the definition of a new drug (other than a drug allowed under the "grandfather clause").

(3) Said declaration cannot lawfully be made in a degree of generality which makes such declaration applicable regardless of the total composition of any drug containing "the same active substances", and of the "conditions prescribed, recommended or suggested in the labeling thereof."

(4) Said declaration cannot lawfully be made so as to ignore, override and set aside the provisions of the "grandfather clause".

(5) Said declaration cannot lawfully be made so as to bind persons not parties to the proceedings and not interested in the specific compounds, "Geroniazol Injection", "Nicozol with Reserpine" and "Nicozol with Reserpine Tablets" covered by NDA 11–742, NDA 10–508 and NDA 11–347.

XIX.

The reasons why such declaration cannot lawfully be made as alleged above are:

(1) Such declaration violates and is not in accordance with the Statutory Law.

(2) The promulgation of the declaration in the proceedings had and held is in excess of the authority of the Food and Drug Administration as granted by Statute.

(3) The promulgation of the declaration in the proceeding had and held is in violation of due process of law in that the Food and Drug Administration failed to follow statutory authority and to afford reasonable, proper and orderly procedures for the determination of the issues, with adequate notice to all affected, and is without observance of procedure required by law.

(4) The promulgation of the declaration in the proceedings had and held is unwarranted by the facts as found and reported therein.

XX.

The plaintiffs are informed and believe that the action of the Food and Drug Administration is a final agency action for which there is no other adequate remedy in a Court.

XXI.

If the asserted position of the Food and Drug Administration is valid, continued manufacture and sale in interstate commerce of said drugs would be in violation of Title 21, Sec. 331, said drugs may be seized under Title 21, Sec. 334, and the plaintiffs and their agents may be subject to criminal penalties under Title 21, Sec. 333.

XXII

The said declaration forces the plaintiffs either to abandon their business of manufacturing and/or selling said drugs, thereby causing them irreparable loss, or to risk the penalties which may be involved should the declaration complained of be found lawful.

XXIII

Each of the plaintiffs has a substantial economic interest in the manufacture and/or sale of these drugs, and will be substantially and irreparably injured if the provisions of the notice set forth in Paragraph X above are enforced.

XXIV

The said drugs are nowhere asserted by the Food and Drug Administration to be harmful.

XXV

The plaintiffs are entitled to a judgment declaring that the declaration herein complained of is invalid. The plaintiffs are further entitled to an order, pending such declaration, enjoining the Food and Drug Administration from implementing said declaration as against the plaintiffs until the Court decides whether such declaration is valid.

WHEREFORE the plaintiffs pray:

(1) That the Court determine the scope, validity and enforceability of the declaration alleged in Paragraph X;

(2) That the Court declare the said declaration to be invalid;

(3) That the Court restrain regulatory proceedings taken pursuant to such declaration until the validity thereof is determined, and that it grant such relief pendente lite;

(4) That the Court grant such further relief as may be proper.

ABRAMS, BOWEN AND TOWNES,
By GEORGE F. TOWNES,
Attorney at Law,
P. O. Box 10128 F. S.,
Greenville, S.C. 29603.
By SOL E. ABRAMS,
Attorney at Law,
P. O. Box 10128 F. S.,
Greenville, S.C. 29603.

Greenville, South Carolina
November 27, 1970

34 F.R. 13673 (August 26, 1969)

Food and Drug Administration

CERTAIN COMBINATION PREPARATIONS CONTAINING PENTYLENETETRAZOL

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences—National Research Council, Drug Efficacy Study Group, on the following drugs:

1. Geroniazol Injection; contains 100 milligrams of pentylenetetrazol and 50 milligrams of nicotinic acid, as sodium nicotinate, per milliliter; by Philips Roxane Laboratories, Division of Philips Roxane, Inc., 330 Oak Street, Columbus, Ohio 43216 (NDA 11–742).

2. Nicozol with Reserpine Tablets; contains 100 milligrams of pentylenetetrazol, 50 miligrams of nicotinic acid, and 0.25 milligram of reserpine per tablet; Nysco Laboratories, Inc., 34–24 Vernon Boulevard, Long Island City, N.Y. 11106 (NDA 10–508).

The Food and Drug Administration concludes there is a lack of substantial evidence that these drugs will have the effects they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in their labeling, as follows:

1. Geroniazol Injection—for use in the treatment of senile confusion, senile depression, senile psychosis, senile fatigue, and senile debilitation.

2. Nicozol with Resperine Tablets—for use in senile psychoses and psychoneuroses, when anxiety and nervous tension are present; and relief of dizzy spells, mental confusion, mild behavioral disorders, irritability, and functional memory defects in elderly patients, in the absence of more serious emotional and psychiatric disturbances.

Accordingly, the Commissioner of Food and Drugs intends to initiate proceedings to withdraw approval of the above-listed new-drug applications.

Prior to initiating such action, however, the Commissioner invites the holders of new-drug applications for these drugs and any interested person who might be adversely affected by their removal from the market, to submit any pertinent data bearing on the proposal within 30 days after publication hereof in the Federal Register. To be considered acceptable for review, the material must be well-organized and consist of adequate and well-controlled studies bearing on the efficacy of the products and must not have been previously submitted.

This announcement of the proposed action and implementation of the NAS-NRC report for these drugs is made to give notice to persons who might be adversely affected by their withdrawal from the market. Promulgation of an order withdrawing approval of the new-drug applications will cause any such drug on the market to be a new drug for which an approved new-drug application is not in effect and will make it subject to regulatory action.

The above-named holders of the subject new-drug applications have been mailed a copy of the NAS–NRC reports and any interested person may obtain a copy on request from the office named below.

Communications forwarded in response to this announcement should refer to "DESI 10508," should be directed to the following appropriate office, and should be addressed to the

Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204:

Requests for NAS–NRC report: Press Relations Office (CE–300). Comments or data regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (MD–16), Bureau of Medicine.

This announcement is issued pursuant to the provisions of the Federal Food Drug and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: August 12, 1969.

HERBERT L. LEY, JR.,
Commissioner of Food and Drugs.

[F.R. Doc. 69–10107; Filed, Aug. 25, 1969; 8:45 a.m.]

35 F.R. 7749 (May 20, 1970)

Food and Drug Administration

[Docket No. FDC–D–177; NDA No. 11–742 et al.]

PENTYLENETETRAZOL-CONTAINING DRUGS

Drugs for Human Use; Drug Efficacy Study Implementation; Notice of Opportunity for Hearing

In an announcement (DESI 10508) published in the Federal Register of August 26, 1969 (34 F.R. 13673), Philips Roxane Laboratories, Division of Philips Roxane, Inc., 330 Oak Street, Columbus, Ohio 43216, and Nysco Laboratories, Inc., 34–24 Vernon Boulevard, Long Island City, N.Y. 11106, the holders of the new-drug applications for Geroniazol Injection (NDA 11–742) containing per milliliter 100 milligrams pentylenetetrazol and 50 milligrams of nicotinic acid, as sodium nicotinate; and Nicozol with Reserpine tablets (NDA 10–508) containing 100 milligrams of pentylenetetrazol, 50 milligrams of nicotinic acid, and 0.25 milligram of reserpine per tablet, respectively, as well as any other interested person, were invited to submit pertinent data bearing on the announced intention to initiate proceedings to withdraw approval of the new-drug applications.

On December 18, 1969, Philips Roxane submitted material for consideration. The material was reviewed and considered together with other available information, does not provide substantial evidence of effectiveness of the drug for the recommended uses in man.

Therefore, notice is hereby given to Philips Roxane Laboratories, Division of Philips Roxane, Inc., and Nysco Laboratories, Inc., and to any other interested person who may be adversely affected by such action, including Hart Laboratories, Station Square One, Paoli, Pa. 19301, holder of NDA 11–347 (Nicozol, with Reserpine Tablets), originally applied for by Drug Specialties, Inc., Winston-Salem, N.C., that the Commissioner of Food and Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of the listed new-drug applications and all amendments and supplements thereto on the grounds that there is a lack of substantial evidence that these drugs have the effect they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in their labeling.

In addition to the new-drug applications listed above, a number of other applications provide for preparations containing pentylenetetrazol for systemic use in humans. Their holders have voluntarily requested withdrawal of approval of those applications, thereby waiving opportunity for hearing; therefore, they are not listed in this notice.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the applicant, and any interested person who would be adversely affected by an order withdrawing such approval, an opportunity for a hearing to show why approval of any new-drug application listed herein should not be withdrawn. Promulgation of the proposed order will cause any drug for human use containing the same active substances to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

Within 30 days after publication hereof in the FEDERAL REGISTER, such persons are required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Office

of the General Counsel, Room 6–62, 5600 Fishers Lane, Rockville, Md. 20852, a written appearance electing whether:

1. To avail themselves of the opportunity for a hearing; or

2. Not to avail themselves of the opportunity for a hearing.

If such persons elect not to avail themselves of the opportunity for a hearing, the Commissioner without further notice will enter a final order withdrawing approval of the new-drug applications. Failure of such persons to file such a written appearance of election within said 30 days will be construed as an election by such persons not to avail themselves of the opportunity for a hearing.

The hearing contemplated by this notice will be open to the public except that any portion concerning a method or process the Commissioner finds entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance.

If such persons elect to avail themselves of the opportunity for a hearing, they must file a written appearance requesting the hearing, giving the reasons why the approval of the new-drug application should not be withdrawn together with a well-organized and full-factual analysis of the clinical and other investigational data they are prepared to prove in support of their opposition. The request must set forth specific facts showing there is a genuine and substantial issue of fact that requires a hearing. If the hearing is requested and justified by the response to this notice, the issues will be defined, a hearing examiner will be appointed, and he shall issue a written notice of the time and place at which the hearing will commence.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052–53, as amended; 21 U.S.C. 355) and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: May 12, 1970.

SAM D. FINE,
Acting Associate Commissioner for Compliance.

[F.R. Doc. 70-6175; Filed, May 19, 1970; 8:45 a.m.]

35 F.R. 14412 (September 12, 1970)

Food and Drug Administration

[Docket No. FDC-D-177; NDA 11-742, etc.]

NYSCO LABORATORIES, INC., AND HART LABORATORIES

Pentylenetetrazol-Containing Drugs for Human Use; Notice of Withdrawal of Approval of New-Drug Application

On May 20, 1970, there was published in the FEDERAL REGISTER (35 F.R. 7749) a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new-drug applications listed therein on the ground that there is a lack of substantial evidence that these drugs have the effect they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in their labeling.

The following firms, listed with their address, respective drug, and new drug application number, have waived opportunity for a hearing on the proposed withdrawal of said new-drug applications in that no response has been received.

NDA No.	Drug name	Applicant's name and address
10-508	Nicozol with Reserpine tablets.	Nysco Laboratories, Inc., 34-24 Vernon Blvd., Long Island City, N.Y. 11106.
11-347	do	Hart Laboratories, Station Square 1, Paoli, Pa. 19301.

The Commissioner of Food and Drugs, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1052, as amended; 21 U.S.C. 355(e)) and under authority delegated to him (21 CFR 2.120), finds on the basis of new information before him with respect to each of said drugs, evaluated together with the evidence available to him when each application was approved, that there is a lack of substantial evidence that each of the drugs will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Therefore, pursuant to the foregoing findings, approval of the above new-drug applications, and all amendments and supplements thereto, is withdrawn effective on the date of the signature of this document. Outstanding stocks of the affected drugs should be recalled.

Dated: September 3, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70-12141; Filed, Sept. 11, 1970; 8:46 a.m.]

[Docket No. FDC-D-177; NDA 11-742 etc.]

PHILIPS ROXANE LABORATORIES

Pentylenetetrazol-Containing Drugs for Human Use; Notice of Withdrawal of Approval of New-Drug Application

On May 20, 1970, there was published in the FEDERAL REGISTER (35 F.R. 7749) a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new-drug applications listed therein on the ground that there is a lack of substantial evidence that these drugs have the effect they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in their labeling.

Philips Roxane Laboratories, Division of Philips Roxane, Inc., holder of NDA No. 11-742 for Geroniazol Injection, 330 Oak Street, Columbus, Ohio 43216, filed a letter requested a hearing pursuant to the May 20, 1970, publication, but did not file any data to support such request. The Commissioner of Food and Drugs concludes there are no genuine and substantial issues of fact to justify a hearing (35 F.R. 7250; May 8, 1970).

The Commissioner of Food and Drugs, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1052, as amended; 21 U.S.C. 355(e)) and under authority delegated to him (21 CFR 2.120), finds on the basis of new information before him with respect to such drug evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented

to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Therefore, pursuant to the foregoing findings, approval of the above new-drug application, and all amendments and supplements thereto, is withdrawn effective on the date of the signature of this document.

Dated: September 3, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70-12142; Filed, Sept. 11, 1970; 8:46 a.m.]

In the United States District Court for the Western District of South Carolina

[Caption Omitted]

AFFIDAVIT

Barrett Scoville, M.D., being first duly sworn, deposes and says:

1. I am the Deputy Director of the Division of Neuropharmacologic Drug Products, Office of Scientific Evaluation, Bureau of Drugs, United States Food and Drug Administration.

2. In connection with the responsibility of this Agency to decide whether new drugs are safe and effective for use by the public, this office reviews and evaluates scientific evidence concerning the safety and efficacy of neuropharmacologic drugs.

3. Following the 1962 amendments to the Federal Food, Drug and Cosmetic Act, as part of the program to implement the new efficacy provision of the Act, the Food and Drug Administration requested the National Academy of Sciences, National Research Council, to have highly qualified, expert panels of scientists evaluate the efficacy of pentylenetetrazol combination drugs offered for senile psychosis and psychoneurosis, with anxiety and nervous tension, senile fatigue, confusion, debilitation, depression, dizzy spells, mild behavioral disorders, irritability and functional memory defects. All available evidence including whatever evidence the NDA sponsors submitted pursuant to the request of FDA, was considered by the NAS-

NRC panels. Their evaluation of these drugs was that they were ineffective for the indicated uses (Exhibit A attached). The Food and Drug Administration, thereafter, also reviewed all of the available evidence concerning these drugs, including the NAS–NRC evaluations, and concluded that there was not substantial evidence to demonstrate that they were effective for the indicated uses. Consequently we commenced proceedings to withdraw approval of all existing new drug applications covering such drugs. There were three such NDAs: NDA 11–742 for Geroniazol injection, held by Philips-Roxane Laboratories, NDA 10–308 for Nicozol with Resperpine, held by Nysco Laboratories, which had been taken over as NDA 11–347, for the same drug, by Hart Laboratories.

4. Notice was published in the Federal Register on August 26, 1969 (34 F.R. 13673, Exhibit B, attached) announcing our conclusion concerning these drugs and inviting the NDA sponsors and any other interested persons to submit any other data they had concerning the effectiveness of these drugs. One firm, Philips-Roxane, submitted data, but it was insufficient and did not alter our conclusion. On May 20, 1970 we published a notice in the Federal Register (35 F.R. 7749, Exhibit C attached) which offered and opportunity for a hearing to the sponsors of the NDA's and any interested person who would be adversely affected by withdrawal of approval of the NDA's. Only one firm requested a hearing (Philips-Roxane), but it failed to provide the required documentation to show that a genuine issue existed which required a hearing for resolution. Notice of withdrawal of the existing NDA's for these pentylenetetrazol combinations was published in the Federal Register on September 12, 1970 (35 F.R. 14412).

5. As part of my official duties I have reviewed the three new drug applications for pentylenetetrazol combinations referred to in paragraph 4, above. Geroniozol is a combination of pentylenetetrazol and nicotinic acid. Nicozol with Reserpine is a combination of pentylenetetrazol, nicotinic acid and reserpine. Both are neuropharmacologic drugs, and are offered for various senile disorders including psychosis, neuropsychosis, fatigue, confusion, debilitation, depression, dizzy spells and other behavioral disorders.

6. Based on my training and experience including my review of the subject new drug applications, my kowledge of the scientific literature, the NAS–NRC evaluation of these drugs, and my professional contacts with other physicians, in this field and on the basis of the information which comes to me in my official capacity as Deputy Director of the Division of Neuropharmacologic Drug Products, Office of Scientific Evaluation, Bureau of Drugs, United States Food and Drug Administration, it is my opinion that pentylenetetrazol, alone, or in combination with nicotinic acid, or nicotinic acid and reserpine, is not now, and never has been, generally recognized, by qualified experts, as both safe and effective for the treatment of senile psychosis or psychoneurosis, with anxiety and nervous tension, senile fatigue, confusion, debilitation, depression, dizzy spells, mild behavioral disorders, irritability, or functional memory defects.

BARRETT SCOVILLE, M.D.

Subscribed and sworn to before me this ——— day of ———, 1970.

———. ———.
Notary Public.

National Academy of Sciences—National Research Council—Division of Medical Sciences

DRUG EFFICACY STUDY

Form A

(To be submitted in duplicate by applicant)

1. NDA Number: 10–508 E–01
2. Date Originally Approved: June 7, 1957
3. Rx X OTC —
4. Brand Name: Nicozol with Reserpine
5. Applicant's Name: Nysco Laboratories, Inc.
   and Address: 3424 Vernon Boulevard, Long Island City, N.Y.
6. Quantitative Formula:

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label):	*Amount (per tablet, per ml., etc.)*
Pentylenetetrazol	100 mg
Nicotinic Acid	50 mg
Reserpine	0.25 mg

7. Dosage Form (tablets, etc.): Tablets
8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Oral
9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).
10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).) We have no additional information than that submitted with our original application.
11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.
12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white). None

NICOZOL

WITH RESERPINE

For Senile Psychoses With Agitation

WHAT IT IS: Pale buff, scored tablets with engraved square.
Each tablet contains:
Pentylenetetrazol—100 mg.
Nicotinic Acid—50 mg.
Reserpine—0.25 mg.

Combines the tranquilizing action of reserpine with the cerebral stimulation (analeptic) and improved behavior produced by Nicozol (pentylenetetrazol and nicotinic acid).

THERAPEUTIC RESULTS: In elderly patients behavior, personal habits, sociability, memory, appearance and general activity are improved. Anxiety and nervous tension are relieved. Other benefits include relief of dizzy spells, mental confusion and irritability.

INDICATIONS: Senile psychoses and psychoneuroses, when anxiety and nervous tension are present. Relief of dizzy spells, mental confusion, mild behavioral disorders, irritability and functional memory defects in elderly patients, in the absence of more serious emotional and psychiatric disturbances. Not recommended in the treatment of hypertension.

DOSAGE: 1 tablet 3 times a day; in severe cases, 2 tablets 3 times a day.

CAUTION: Federal law prohibits dispensing without prescription.

CONTRAINDICATIONS: Should not be given to patients within 3 days prior to use of electroconvulsive treatment or those receiving intravenous injections of pentylenetetrazol. Discontinue medication in the event that muscular twitchings or clonic convulsions occur. Dosage should be reduced or discontinued if nasal congestion, nausea, vomiting, diarrhea or mental depression occur. Mental depression and peptic ulcer are relative contraindications to the use of reserpine. In such cases NICOZOL with RESERPINE should be used with caution.

The flush experienced by sensitive individuals is not detrimental and is part of the nicotinic acid therapy. There may be an occasional case of pruritus due to nicotinic acid.

SUPPLIED: Bottles of 100, 1000 tablets.

February 1962

HART LABORATORIES

Division of A. J. Parker Company, Winston-Salem, N.C.

NICOZOL
NDA 10508
LOG 2660

PANEL ON PSYCHIATRIC DRUGS

INDICATIONS

1. Nicozol (reserpine) is indicated as useful in senile psychoses, when anxiety and nervous tension are present

EVALUATION: Ineffective.

COMMENTS: Nicozol with Reserpine is a combination of pentylenetetrazol and nicotinic acid with reserpine. Pentylene-

tetrazol and nicotinic acid form the combination known as Geroniazol, which has been evaluated as "Ineffective" by the Panel in the treatment of senile confusion, with the following comment:

> (From DES Evaluation of Geroniazol, NDA 11742, Log 653). Many uncontrolled studies claim efficacy for oral Metrazol, and a few for nicotinic acid in geriatric organic psychoses and confusional states. One small controlled study of i.v. medication shows a trend favoring the oral form over the i.v., and the i.v. over placebo. Two controlled studies that are small, with rather weak and inappropriate criteria and methods for evaluating clinical improvement, favor Metrazol (1,3). The only study of i.v. medication in nonsenile depression shows little efficacy (three of 18 improved). There is no evidence presented on treatment of fatigue or psychosis in other than senile conditions.

DOCUMENTATION:

1. Mead, S., E. E. Mueller, E. P. Mason, T. Kheim, and W. B. Kountz. A study of the effects of oral administration of metrazol in old individuals. J. Geront. 8:472–476, 1953.

2. Pacella, B. L., J. Doltolo, and R. R. Cerulli. Subconvulsive metrazol therapy. J. Nerv. Ment. Dis. 117:50–54, 1953.

3. Swensen, W. M., and B. P. Grimes. Oral use of metrazol in senile patients. Geriatrics 8:99–101, 1953.

In general, the use of reserpine in the treatment of major psychoses has been established. Dosages in the treatment of psychoses are rarely less than 1 mg/day, whereas those used in the treatment of hypertension rarely exceed 1 mg/day.

With the advent of the phenothiazines, the use of reserpine as an antipsychotic medication has declined, although it still has a rational basis in antipsychotic therapy. Many studies show reserpine to be more effective than placebo in the treatment of psychoses.

The Panel accordingly evaluated the combination known as Nicozol with Reserpine as "Ineffective" for this indication. In addition, the Panel finds the wording of the indication imprecise and suggests the deletion of the phrase "nervous tension."

II. Nicozol (reserpine) is indicated as useful in psychoneuroses, when anxiety and nervous tension are present

EVALUATION: Ineffective.

COMMENTS: The Panel feels that the efficacy of reserpine and reserpine compounds in the treatment of anxiety has not been established. Since the introduction of reserpine, a number of representatives of several classes of drugs with more conventional sedative properties have been introduced and found to be effective—to the extent that drugs are—in the treatment of anxiety. Although reserpine exerts some effect in calming the anxious patient, the concomitant risk of reserpine's depression-producing effect should be noted. It is the Panel's judgment that—in the general practice of psychiatry today—the use of reserpine as an antianxiety agent is obsolete.

The treatment of anxiety with drugs is complicated by many non-drug factors (5), such as the personality of the patient, his relationship to the physician, and innumerable and varying social and environmental factors. Claims for the effectiveness of reserpine and reserpine compounds in producing sedation and reducing tension represent as yet poorly differentiated general effects of calming and tranquilization, specific definitions are not supported in the literature cited by the manufacturers. In addition, the literature is scanty and poorly documented, relying on predominantly uncontrolled studies.

See also Comments for Indication I.

Because there is no evidence presented for the efficacy of nicotinic acid and pentylenetetrazol as antianxiety agents, the Panel evaluates the combination "Ineffective" for this indication. In addition, the Panel finds the wording of the indication imprecise and suggests the deletion of the phrase "nervous tension."

DOCUMENTATION:

1. Davis, J. M. Efficacy of tranquilizing and antidepressant drugs. Arch. Gen. Psychiat. (Chicago) 13:552–572, 1965.

2. Ferguson, R. S. A. clinical trial of reserpine in the treatment of anxiety. J. Ment. Sci. 102:30–42, 1956.

3. Hauck, P., H. Phillips, and R. Armstrong. The effects of reserpine on psychotic patients of varying degrees of illness: a pilot study. J. Clin. Psychol. 13:188–190, 1957.

4. Lemieux, G. A. Davignon, and J. Genest. Depressive states during rauwolfia therapy for arterial hypertension; a report of 30 cases. Canad. Med. Assoc. J. 74:522–526, 1956.

5. Rickels, K., Ed. Non-specific factors in drug therapy. Non-specific Factors in Drug Therapy of Neurotic Patients. Springfield: Charles C. Thomas, 1968.

GENERAL COMMENTS

The Panel finds the following statement in the package insert vague and too general and suggests its deletion from the package insert:

Relief of dizzy spells, mental confusion, mild behavioral disorders, irritability and functional memory defects in elderly patients, in the absence of more serious emotional and psychiatric disturbances.

Approved by _____ _____,
Chairman.

DIVISION OF MEDICAL SCIENCES

DRUG EFFICACY STUDY

Form A

(To be submitted in duplicate by applicant)

1. NDA Number: 11–742 E–01 2. Date Originally Approved: 1–19–59 1315 3. Rx X OTC.
4. Brand Name: GERONIAZOL Injection
5. Applicant's Name: Philips Roxane Laboratories, Division of Philips Roxane, Inc.
and Address 330 Oak Street, Columbus, Ohio 43216
6. Quantitative Formula

Established (Non-Proprietary) Name of Active Ingredients (in order shown on label) : Each ml. contains :	*Amount (per tablet, per ml., etc.)*
Pentylenetetrazol	100 mg.
Nicotinic Acid (as thw sodium salt)	50 mg.

7. Dosage Form (tablets, etc.) Sterile injection

8. Route of Adm. (Oral, etc. Where a new drug application covers different routes of administration, separate forms should be used.) Subcutaneously, intramuscularly, intravenously.
9. Therapeutic Claims—Attach 10 labels and 10 package inserts (if used) to original Form A (blue) and 1 copy to duplicate Form A (white).
10. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, the package insert, or brochure. Approximately 5 to 10 key references are requested, if available. (Attach 10 copies to original Form A (blue) and 1 copy to duplicate Form A (white).) NONE
11. The applicant is invited, if he so desires, to submit any unpublished material that is pertinent to the evaluation of the drug by the Academy—Research Council. This supplementary material should be packaged with Form A (white). A single copy of this material is requested.
12. In this space, please list and describe briefly the supplementary material that is submitted with Form A (white). NONE

Similar results were obtained with parenterally administered nicotinic acid by Gregory (10), Washburn (11) and Moore (12) in senile and arteriosclerotic psychoses. The importance of early treatment is again stressed (10).

In view of the documented success of both pentylenetetrazol and nicotinic acid parenterally administered, their presentation together in a single injectable dosage form is highly rational and should produce a greater mutual enhancement of their respective therapeutic actions and speedier response than demonstrated by their concurrent oral administration. The supplementation of oral therapy by the parenteral dosage form can be expected to produce greater and more rapid therapeutic success in the treatment of senile confusion, depression, psychosis, fatigue and debilitation.

CONTRAINDICATIONS

In patients with a history of epilepsy, hemorrhagic pulmonary tuberculosis, acute brain injury and weakness of the bony system.

PRECAUTIONS

Intravenous injection should be reserved for severe cases or those not responding to subcutaneous or intramuscular doses, and only administered with the patient in bed or lying down. Dosage should not be repeated in less than 2 to 3 hours. The patient should not be released in less than 20 minutes after injection. Intravenous dosage above 2 cc., especially if rapidly administered may produce a convulsion and unconsciousness lasting from 5 to 15 seconds. Overdosage is indicated by a slight twitching of the face and body or blacking out of the patient, but effects are dissipated in a short time. When necessary, convulsions may be readily arrested by intravenous barbiturates.

DOSAGE AND ADMINISTRATION

Subcutaneously: 1 cc. Intramuscularly; 1 to 2 cc. Intravenously; initially 1 cc. *injected slowly.* If no reaction (other than flushing) occurs, increase on subsequent days by increments to 2 cc.

Best results are obtained by administering 2 or 3 times weekly for several weeks, then once a week for 2 to 3 months, depending on the response of the patient.

SUPPLIED

AM–175, 10cc. Multiple Dose Vial

References

(1) Levy, S.; J.A.M.A., *153*:1260, 1953.
(2) Thompson, J. and Proctor, R. C.; No. Carolina M. J. *51*:596, 1954.
(3) Seidel, H. et al; J. Am. Geriatrics Soc., *1*:280, 1953.
(4) Sal y Rosas, F.; through J.A.M.A., *119*:378, 1942.
(5) Hirschmann, J.; Deutsche Med. Wchnschr., *74*:513, 1949.
(6) Leroy, A.; J. belge neruol, Psychiat., *38*:613, 1938.
(7) Lieberman, A. L.; Geriatrics, *9*:125, 1954.
(8) Paccila, B. et al; J. Nerv. & Ment. Dis. *117*:50, 1953.
(9) Lieberman, A. L. et al; Geriatrics, *9*:371, 1954.
(10) Gregory, I.; Am. J. Psychiat., *108*:838, 1952.
(11) Washburne; Ann. Int. Med., *32*:261, 1950.

(12) Moore, D. F. et al; J. Clin. & Exper. Psychopath, *12*:249, 1951.

Philips Roxane Laboratories

Division of Philips Roxane, Inc.
Columbus, Ohio, U.S.A.

Geroniazol Injectable

COMPOSITION

Each cc. contains:

Pentylenetetrazol	100 mg.
Nicotinic Acid (as the sodium salt)	50 mg.
Benzyl Alcohol (preservative)	1.5%

INDICATIONS

In the treatment of senile confusion, depression, psychosis, fatigue and debilitation.

Geroniazol injectable presents in parenteral form the therapy originally introduced by Levy (1) and since confirmed by Thompson (2), Seidel (3) and others, as an effective oral treatment in senile confusion and mental deterioration. The pharmacological basis of this therapy is the combatting of cerebral anoxia through the respiratory and circulatory stimulant actions of pentylenetetrazol and the peripheral vasodilator action of nicotinic acid.

Ample evidence is available (4–12), indicating that a more rapid and profound response in these and other conditions can be expected by the parenteral administration of this therapy alone, or in conjunction with oral administration.

Sal y Rosas (4), Hirschmann (5) and Leroy (6) reported that injections of pentylenetetrazol in moderate (sub-convulsive) dosage were extraordinarily helpful in the treatment of anxiety neuroses, endogenous depression, and melancholia, particularly in early cases, Lieberman (7,9) and Pacella (8) obtained highly encouraging results from the employment of i.v. injections of sub-convulsive doses of pentylenetetrazol in geriatric patients with arteriosclerotic mental changes, with greatest success being found in early cases. The response was much more rapid than that obtained with oral pentylenetetrazol (9).

This drug has been evaluated by the following Panels:

1. Panel on Psychiatric Drugs
2. Panel on Drugs Used in Anesthesiology
3. Panel on Drugs Used in Respiratory Disturbances

Evaluations follow:

Panel on Psychiatric Drugs

INDICATIONS

I. Geroniazol Injection is used in the treatment of senile confusion

EVALUATION: Ineffective.

COMMENTS: Many uncontrolled studies claim efficacy for oral Metrazol, and a few for nicotinic acid in geriatric organic psychoses and confusional states. One small controlled study of i.v. medication shows a trend favoring the oral form over the i.v., and the i.v. over placebo. Two controlled studies that are small, with rather weak and inappropriate criteria and methods for evaluating clinical improvement, favor Metrazol (1,3). The only study of i.v. medication in nonsenile depression shows little efficacy (three of 18 improved). There is no evidence presented on treatment of fatigue or psychosis in other than senile conditions.

DOCUMENTATION:

1. Mead, S., E. E. Mueller, E. P. Mason, T. Kheim, and W. B. Kountz. A study of the effects of oral administration of metrazol in old individuals. J. Geront. 8:472–476, 1953.

2. Pacella, B. L., J. Doltolo, and R. R. Cerulli. Subconvulsive metrazol therapy. J. Nerv. Ment. Dis. 117: 50–54, 1953.

3. Swenson, W. M., and B. P. Grimes. Oral use of metrazol in senile patients. Geriatrics 8:99–101, 1953.

II. Geroniazol Injection is used in the treatment of senile depression

EVALUATION: Ineffective.

COMMENTS: Same as for Indication I.

DOCUMENTATION: Same as for Indication I.

III. Geroniazol Injection is used in the treatment of senile psychosis

EVALUATION: Ineffective.
COMMENTS: Sale as for Indication I.
DOCUMENTATION: Same as for Indication I.

IV. Geroniazol Injection is used in the treatment of senile fatigue

EVALUATION: Ineffective.
COMMENTS: Same as for Indication I.
DOCUMENTATION: Same as for Indication I.

V. Geroniazol Injection is used in the treatment of senile debilitation

EVALUATION: Ineffective.
COMMENTS: Same as for Indication I.
DOCUMENTATION: Same as for Indication I.

GENERAL COMMENTS

There is no rationale for the parenteral use of this preparation.

Approved by

_____,
Chairman,

PANEL ON DRUGS USED IN ANESTHESIOLOGY

INDICATIONS

I. Geroniazol is indicated as an analeptic

EVALUATION: Ineffective.
COMMENTS: The suggested indications are senile confusion, depression, psychosis, fatigue, and debilitation. Geroniazol is claimed to exert its action through respiratory and circulatory stimulation and vasodilation. The beneficial effect of this combination of two drugs, pentylenetetrazol and nicotinic acid, is credited to the respiratory and circulatory stimulant actions of pentylenetetrazol and the peripheral vasodilator action of nicotinic acid.

There is no evidence, direct or indirect, to support either the mechanism of action or the action itself. Consequently, Geroniazol must be judged ineffective as an analeptic. This drug has had no proper clinical evaluation.

DOCUMENTATION: None.

GENERAL COMMENTS

The insert gives 12 references to the use of the product. On a separate list are 24 references to the use of pentylenetetrazol, three to the use of nicotinic acid, and two more to the use of Geroniazol.

Of the 41 references, none qualifies as proper drug evaluation. Two papers give more information than the rest.

(1) Lieberman, A. L. et al: Evaluation of intravenous and oral use of metrazol in hospitalized arteriosclerotic psychiatric patients. Geriatrics 9:371, 1954.

This is a comparative study of the effect of pentylenetetrazol (not Geroniazol) and a placebo in 41 arteriosclerotic phychiatric patients. The evaluation was by psychologic testing and clinical impression. The authors found improvement by clinical impression in one-third and one-half of the patients in the two treated groups, and in one-fourth of the patients receiving placebo. There was no change by psychologic testing.

(2) Levy, S.: Pharmacological treatment of aged patients in a state mental hospital. JAMA 153:1260, 1953.

This is a study of 30 patients, most of them suffering from the chronic brain syndrome. The effect of Geroniazol is compared with that of a placebo in a double-blind study. The results are not presented in sufficient detail to permit evaluation; no statistical analysis is done. The author claims marked improvement in behavior and a better performance on psychologic testing.

The Panel has been unable to find any relevant controlled studies in man of either Geroniazol, pentylenetetrazol, or nicotinic acid.

Approved by

_____, *Chairman.*

PANEL ON DRUGS USED IN RESPIRATORY DISTURBANCES

INDICATIONS

I. Respiratory stimulation

EVALUATION: Ineffective.

COMMENTS: This compound acts as a general central nervous system stimulant, and this indirectly results in some respiratory stimulation. In the opinion of the Panel, this effect is too transient (because of rapid inactivation) for pentylenetetrazol to be an effective respiratory stimulant itself. However, any respiratory stimulation that may occur does so at a cost of increased oxygen consumption and carbon dioxide production.

DOCUMENTATION:

1. Curran, T.R., and D.K. Phelps. Sustained release pentylenetetrazol-nicotinic acid therapy in senile patients. Amer. Practit. 11:617–619, 1960.

2. Esplin, D.W., and B. Zablocka. Central nervous system stimulants; I. Strychnine, picrotoxin, pentylenetetrazol, bemegride, nikethamide, and miscellaneous agents (ethamivan, flurothyl), pp. 345–353. In L.S. Goodman and A. Gilman, Eds. The Pharmacological Basis of Therapeutics. (3rd ed.) New York: The Macmillan Co., 1965.

Approved by

SOL KATZ,
Chairman.

36 F.R. 3372 (February 23, 1971)

Food and Drug Administration

DRUGS FOR HUMAN USE

New Drugs on the Market Without Approved New-Drug Applications; Statement of Policy

The Food and Drug Administration is seriously concerned about the continued introduction into the market of new products without submission and approval through the new-drug procedures of the Federal Food, Drug, and Cosmetic Act. This appears to result from a misunderstanding of the new-drug

requirements or from a deliberate effort to avoid the new drug procedures.

The Commissioner wishes to make it entirely clear that he will require strict adherence to the new-drug requirements. Anyone introducing a new product, or an old product for a new use, or a new combination of old ingredients, or any other product that is or may be a "new drug" under section 201(p) of the Act, and the interpretations provided thereunder by regulations and court decisions, must submit and obtain new-drug approval prior to marketing the preparation. Should a manufacturer or distributor undertake to decide unilaterally that any such product does not require new-drug approval, he must recognize that he risks criminal and civil regulatory action, as well as a probable recall of the product from the market. The burden will be upon such a person to establish that there was, and that he acted upon, a body of published medical data, available to experts in the medical profession generally, from which such experts could fairly and responsibly reach a conclusion that the safety and effectiveness of the particular preparation for the conditions for which it is intended have been so well documented that the composition of the product is such that it would be generally recognized as both safe and effective for the conditions for which the drug is prescribed, recommended, or suggested in its labeling.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 505, 701(a), 52 Stat. 1041–42, as amended, 1052–53, as amended, 1055; 21 U.S.C. 321(p), 355, 371(a)) and under authority delegated to the Commissioner (21 CFR 2.120), it is proposed that the following new section be added to Subpart A of Part 130:

§ 130. - - - - NEW DRUGS ON THE MARKET WITHOUT APPROVED NEW-DRUG APPLICATIONS

(a) The Food and Drug Administration published a statement of policy on May 28, 1968 (33 F.R. 7758), § 130.39 (21 CFR 130.39), revoking all opinions theretofore given that an article was "not a new drug" or was "no longer a new drug." That policy states that undisclosed or unreported side effects, as well as the emergence of new knowledge presenting questions with respect to the safety or effectiveness of a drug, may result in its being a "new drug" even though it may previously have been considered "not a new drug." The Food and Drug

Administration is publishing its requirements for continued marketing of these and other drugs through the process of implementing the conclusions of the NAS/NRC Drug Efficacy Study on labeling claims made for drugs marketed under the new-drug and antibiotic drug procedures between 1938 and 1962.

(b) In implementing the conclusions of the Drug Efficacy Study and identifying all marketed drugs affected by this review, it is apparent that large numbers of drugs have been, and continue to be, introduced to the market without clearance through the new-drug procedures and without the manufacturer or distributor having reached an understanding with the Food and Drug Administration that new-drug approval is not required. These include products with new formulations, new manufacturers, new manufacturing procedures, and new or revised claims. Most, if not all of these products are new drugs and should have been cleared through the new-drug procedures prior to marketing.

(c) The marketing of a new drug based on a conclusion by the manufacturer or distributor that the drug does not fall within the statutory definition of a "new drug" because its composition is such that the particular drug would be generally recognized among appropriately qualified experts as safe and effective for its labeled indications is a risk that may ultimately result in injury to patients or ineffective treatment, and may subject the manufacturer or distributor to civil and criminal liability and to product recall. The manufacturer or distributor must be prepared to support any such unilateral decision by the medical documentation upon which it can be concluded by qualified experts that the safety and effectiveness of the drug for the conditions for which it is intended are so well established that the product would be generally recognized as safe and effective for the conditions for which it is labeled.

(d) The determination whether a drug is generally recognized as safe and effective for any condition is complex and not an absolute or one-time determination. The judgment requires consideration of the composition of the drug in terms of its reproducibility and reliability, as well as the indications for its use. Since product reproducibility and reliability require adherence to the conditions of current good manufacturing practice, including when applicable assurance of bioavailability, there are few if any times that an expert judgment can be

reached without full knowledge of factors that affect product composition. This consideration alone means that new-drug approval will be required in essentially all cases. The judgment is affected by new knowledge pertaining to adverse effects from the drug and by new considerations applicable to the treatment of the condition or disease involved. Full information necessary to sustain an expert judgment as to safety and effectiveness of a drug may not be available to the manufacturer or distributor or to the experts upon whom he relies. The Food and Drug Administration believes that before a manufacturer or distributor introduces a product to the market, whether or not the same or a simular product is already marketed by another firm, a request for review and comment on the proposal should be submitted. Information submitted should include a complete statement of the composition (active and inactive ingredients, and assurance of product reliability), the labeling, and an adequate summary of the medical documentation on which the manufacturer or distributor and his expert advisors have reached a decision that the composition of the drug is such that it is generally recognized as safe and effective for the conditions for which it is to be prescribed, recommended, or suggested in its labeling.

(e) Manufacturers and distributors of drugs on the market which have not been cleared through the new-drug procedures should undertake an immediate study of all such drugs, their composition, their labeling, and the available evidence of safety and effectiveness upon the basis of which the products have been marketed. Appropriate steps should be taken to remove from the market drugs not supported by adequate evidence of safety and effectiveness and to bring all drugs that are to remain on the market into full compliance, including compliance with the new-drug provisions. The Food and Drug Administration is prepared to give advice on all drugs upon written inquiry setting forth the complete composition, the labeling, and an adequate summary of the medical documentation supporting the safety and effectiveness of the product.

Interested persons may, within 30 days after publication hereof in the FEDERAL REGISTER, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-62, 5600 Fishers Lane, Rockville, Md. 20852, written comments (preferably in quintuplicate) regarding this proposal. Com-

ments may be accompanied by a memorandum or brief in support thereof.

Dated: February 17, 1971.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.71-2414 Filed 2-22-71;8:46 am]

[Original filed, February 10, 1971, Miller C. Foster, Jr., clerk]

In the District Court of the United States for the District of South Carolina, Greenville Division

Civil Action No. 70-1001

[Caption omitted]

ORDER

This is a civil action for declaratory and injunctive relief brought by twenty-four pharmaceutical companies aggrieved by the action of the Food and Drug Administration (hereinafter F.D.A.) respecting drugs containing pentylenetetrazol. The events leading to the commencement of this action may be summarized as follows: In August 1969 the F.D.A. announced in the FEDERAL REGISTER its intention to initiate proceedings to withdraw approval of new drug applications for two drugs containing pentylenetetrazol and nicotinic acid. (34 F.R. 13673) The drugs covered by those applications differed from those manufactured by the plaintiffs herein in that the product covered by one application was injected intravenously and the other application contained a third active ingredient, reserpine. The published notice invited the submission of data on the efficacy of the products by any interested person who might be adversely affected by the removal from the market of the drugs covered by the new drug applications. The notice further stated:

> Promulgation of the proposed order will cause any drug for human use containing the same active substances to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

None of the plaintiffs herein responded to the notice and in May 1970, a second notice was published stating that substantial evidence of the effectiveness of the drugs covered by the new drug applications had not been provided and that the the approval of the application would be withdrawn. Notice was also given that any affected person desirous of a hearing on the question should so elect within 30 days (35 F.R. 7749). That notice contained language concerning the effect on drugs other than those covered by the applications to be withdrawn substantially identical to the language of the August notice set out above.

In September 1970 the F.D.A. published its order withdrawing approval of the two new drug applications mentioned above and directing the recall of outstanding stocks of the drugs. 35 F.R. 14412.

Pursuant to its revocation of the two new drug applications, the F.D.A. took steps to effect the removal from the market of drugs containing pentylenetetrazol manufactured by various of the plaintiffs. By their complaint in this action the plaintiffs seek declaratory judgment determining the validity and enforceability of the order of the Secretary as it concerns their drugs and injunctive relief pendente lite. The defendants moves that the action be dismissed for want of jurisdiction and failure to state a claim for which relief can be granted.

The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, *et seq.*) effective in 1938, gave preclearance authority to the Food and Drug Administration to regulate the distribution of new drugs by a system of new-drug applications which had to be obtained before distribution of the drug in interstate channels was allowed. The early definition of new drugs, however, gave the Agency power to regulate these drugs and approve them on the basis of safety alone. The drug companies were not required to support their claims of effectiveness for the drug with appropriate medical data. Effective on October 10, 1962, the Act was amended to close this important gap in the regulatory power of the Agency. Under the provisions of the Act as amended, a drug not only must be proved safe, but also must be shown by "substantial evidence," to be effective for the indication and uses described in its labeling. The amendments also define "substantial evidence" as consisting of "... adequate and well-controlled investigations, including clinical investigations, by experts . . ." sufficient to demonstrate that the drug

works as claimed. [21 U.S.C. 355(d)]. The burden of producing evidence of effectiveness to support continued marketing of drugs which have already been cleared on the grounds of safety, is placed squarely on the drug manufacturers and distributors. [21 U.S.C. 355(b)]. The Act as amended also gives the Secretary power to revoke approved new drug applications for several reasons among which is failure to submit substantial evidence of the effectiveness of the drug [21 U.S.C. 355(e)3]. It was pursuant to this authority that the Secretary issued the order by which the plaintiffs herein are aggrieved.

The Act grants the Secretary primary jurisdiction to make determinations regarding new drug applications and provides direct appeal from his orders to the circuit courts.[1]

The plaintiffs do not contend that this court has jurisdiction to consider the propriety of the Secretary's revocation of the

[1] 21 U.S.C. § 355(h). An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 23, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the Court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

two new drug applications. Rather they argue either that their drugs are not new drugs within the meaning of the Act or are within the grandfather clause; [2] and are therefore not subject to the Secretary's regulation of new drugs. The plaintiffs contend that seizure, injunction, or criminal prosecution by the F.D.A. pursuant to 21 U.S.C. §§ 332–34 is imminent.[3] They urge that, rather than proceeding at their peril, they are entitled to declaratory relief adjudicating the merits of their respective contentions concerning the status of their drugs.[4] They

[2] 21 U.S.C. § 321(p). The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigation, been used to a material extent or for a material time under such conditions.

[3] The plaintiff Bentex Pharmaceutical Company received the following letter from F.D.A.:

Nov. 4, 1970.

"This letter is written in reference to your products Benizol Tablets & Elixir, Benizol A–D Tablets, & Benizol Plus capsules & Elixir containing Pentylenetetrazol for human use.

"On September 12, 1970, an announcement published in the *Federal Register* setting forth the conclusion of the Food and Drug Administration that there is a lack of substantial evidence that drugs similar to yours are effective for the uses prescribed, recommended, or suggested in their labeling.

"Accordingly, the Commissioner of the Food and Drug Administration has withdrawn approval of the applicable new drug applications for such drugs.

"The withdrawal of all previously approved new drug applications causes any similar drug to be a new drug for which an approved new drug application is not in effect. Because these are no longer regarded as legal products, any such drug on the market is subject to regulatory proceedings under the applicable provisions of the Federal Food, Drug, and Cosmetic Act.

"We request your reply within 15 days after receipt of this letter stating your intentions with respect to removal of all outstanding stocks of your product to the retail level."

[4] It appears that for a time drugs of the type in question were regarded as old drugs by the F.D.A. The record contains a letter dated Dec. 15, 1958 which reads in pertinent part as follows: "As to your inquiry

argue persuasibly that they are entitled to a day in court on that question prior to the seizure of their products and possible criminal prosecution.

The plaintiffs urge that they can only have that day in this court. The court does not agree. The Act gives the F.D.A. authority to proceed by seizure action, criminal prosecution, or injunction, [21 U.S.C. 332–334] to clear the channels of interstate commerce of drugs which have improperly avoided the new drug procedures. This grant of authority to approve or withhold approval of new drug application, or to proceed with regulatory action in the courts, necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which requires an approved new drug application for lawful interstate shipment. The determination that drug is a new drug is essential to any F.D.A. action regulating it by means of new drug applications. Therefore, the F.D.A. must have jurisdiction to make that determination.[5]

The defendant, on the other hand, urges that this court does not have jurisdiction to consider and determine the status of the drugs in question, that the F.D.A. has primary and exclusive jurisdiction with appeal to the circuit court. That contention is likewise without merit. There is no doubt that the F.D.A. does have primary jurisdiction to make determinations concerning the safety and effectiveness of new drugs. Its expertise is necessary for consideration of the complex and technical nature of the factual issues to be evaluated.[6] That question is not, however, in dispute in this instance. The contention urged by the plaintiffs that its drugs are old or grandfathered, must turn upon the court's conclusion as to whether among qualified experts there was general recognition of the

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concerning the new drug status of a timed disintegration tablet containing Pentylenetetrazol 300 mg., Nicotinic Acid 150 mg. In our opinion this article is not a new drug as defined in section 201(p) of the Federal Food, Drug, and Cosmetic Act when distributed as a prescription preparation under the labeling which you have submitted." Statements such as the above were, however, revoked by the Secretary [21 C.F.R. 130.39].

[5] Hymson, Wescott and Dunning, Inc. v. Finch, C.A. 2112, D. Md., decided September 16, 1970, on facts represented to the court to be similar to the present case held that the F.D.A. could consider and decide questions determining the status of a drug and that review of that determination would be available pursuant to 21 U.S.C. 355(h) set out at n. 1, supra.

[6] See e.g. Far East Conference v. United States, 342 U.S. 570 (1952); Tyler Pharmacal Dist. v. H.E.W., 408 F. 2d 95 (7th Cir. 1969); Lemmon Pharmacal Co. v. Richardson, C.A. 68–921, E.D. Pa. 1970.

safety and efficacy of the drug. [*United States* v. *"Quick-O-Ver"*, 274 F. Supp. 443 (1967)]. Counsel for the defendants acknowledged that the fact that the drugs were old or grandfathered would be a defense to be raised and considered in the district court when and if the F.D.A. sought sanctions against the plaintiff manufacturers.

The remaining question regarding the jurisdiction of this court is whether the action for declaratory judgment may be maintained in its present posture. The opinions of the Supreme Court in *Abbott Laboratories* v. *Gardner*, 387 U.S. 136 (1967) and *Toilet Goods Asso.* v. *Gardner*, 387 U.S. 158 (1967) convince this court that the present matter is properly before it. As pointed out in those cases, there is nothing in the Food, Drug and Cosmetic Act [21 U.S.C. § 301, *et seq.*] which bars a pre-enforcement suit under the Administrative Procedure Act [5 U.S.C. §§ 701–704] and the Declaratory Judgment Act [28 U.S.C. § 2201]. The language in the Secretary announcement of May 20, 1970, of which the plaintiffs complaint and pursuant to which the Secretary apparently intends to proceed against them, is apparently final within the meaning of 5 U.S.C. § 704. (*Abbott*, supra, at 692) The letter of the F.D.A. set out above in note 4, indicates that action against the plaintiffs is imminent. The affidavits of the plaintiffs show that the threatened action will result in substantial injury to them. Therefore, this matter is properly before this court and the defendant's motion to dismiss is denied.

The court indicated above that the F.D.A. has jurisdiction to determine whether the drugs in question are new drugs. The court is of the opinion that, even though that determination can be made in this forum, the nature of the proof relevant to that issue makes the F.D.A. the more able arbiter of the question. However, if such determination is to be binding upon the plaintiffs in this action and the industry in general, parties interested in the status of drug combinations must be given an opportunity to be heard. They must be provided a day in court on the issue, during which a record can be made, on which record appeal to the circuit court can be had. That procedure would produce a resolution to the question which would bind the industry and remove the issue from subsequent, and perhaps numerous, enforcement actions. These plaintiffs quite properly point out that they have as yet had no opportunity to be heard on the question of whether their products are new drugs within the meaning of

the Act; and it does not appear that such hearing could have been required of the F.D.A. by the plaintiffs. Evaluation of conflicting reports as to the reputation of drugs among experts in the field is not a matter well left to a court without chemical or medical background. The court's opinion in this regard has influenced it considerably in its consideration of appropriate temporary relief.

The area of regulation of drugs is one which the court enters with great reluctance. However, the affidavits of the plaintiffs convince the court that they may suffer substantial business losses, perhaps unnecessarily, if the court refuses to grant temporary relief. As the court understands the record before it and the argument of counsel, there is no contention that the use of the plaintiff's drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs. The court's order, being based upon this hypothesis, will be vacated upon a sufficient contrary showing by the defendant and, upon request by the defendant, the court will arrange to hear its proof in that regard.

The situation revealed by the record to date convinces the court that the status quo must be preserved until such time as the plaintiffs have an opportunity to be heard on the merits of their contention. Therefore, the court will enjoin the defendants from instituting actions against the plaintiffs on account of such of their products as are presently marketed, as contain combinations of pentylenetetrazol and nicotinic acid, are distributed by prescription, and are for treatment of symptoms of senility in geriatric patients; and the defendants are hereby enjoined from instituting any action against the plaintiffs herein for the cause stated above until such time as there has been a determination that the products in question are new drugs. Recognizing the desirability of the F.D.A.'s making such determination, after a hearing of the matter, this court will defer further proceedings herein upon a showing by the defendants that such hearing will be held. It will dissolve the injunction herein ordered, and dismiss the presentation upon resolution of the question by the F.D.A. after a hearing.[7] Should the F.D.A.

[7] A court has considerable discretion in proceeding in actions for declaratory judgment, and may dismiss such actions if they are pending in litigation elsewhere. Abbott Laboratories v. Gardner, 387 U.S. 136, 155 (1952).

decline to hold such hearing, the matter must proceed to determination in this court.

And *It is so ordered.*

Robert W. Hemphill
ROBERT W. HEMPHILL,
United States District Judge.

Columbia, South Carolina. FEBRUARY 10, 1971.

[A true copy.
Teste:

MILLER C. FOSTER, Jr.
Clerk, by: Deputy Clerk.]

In the United States Court of Appeals for the Fourth Circuit

No. 71-1243

BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMACEUTICAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC., SOUTHERN DRUG & MFG. CO., THE BLAINE COMPANY, BROWN PHARMACEUTICAL CO., MAYRAND, INC., PHARMACEUTICAL ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHARMACEUTICALS, INC., BCR PHARMACAL CO., INC., ALTO PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES, INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMACEUTICAL PRODUCTS, INC., FOS PHARMACEUTICAL CO., W. E. BOODY & CO., APPELLANTS

v.

ELLIOT P. RICHARDSON, SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, APPELLEES

Appeal From the United States District Court for the District of South Carolina, at Greenville. Robert W. Hemphill, District Judge

Argued December 8, 1971—Decided May 23, 1972

Before WINTER, RUSSELL, and FIELD, Circuit Judges

George F. Townes (*Sol E. Abrams* on brief) for Appellants, and *Charles R. McConachie*, Attorney, Department of Justice

(*Will Wilson*, Assistant Attorney General, *John L. Murphy*, Chief, Administrative Regulations Section, *William W. Goodrich*, Assistant General Counsel, Food, Drugs, and Environmental Health Division, *Robert N. Anderson*, Attorney, United States Department of Health, Education, and Welfare, and *Howard S. Epstein*, Attorney, Department of Justice, on brief) for Appellees.

RUSSELL, *Circuit Judge:* This appeal turns on a construction of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1962.[1] 21 U.S.C. 301, *et seq.* This statute requires pre-marketing approval and clearance of any "new drug" by the Secretary of Health, Education, and Welfare.[2] The term "new drug" is defined as one "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof * * *."[3] From a denial of a pre-marketing approval or a withdrawal of a previously given approval, an appeal, originally to the District Court, now to the Circuit Court of Appeals, is authorized.[4] Drugs, which do not fit the definition of a "new drug" do not require FDA clearance for marketing. There is no provision in the Act for administrative determination whether a particular drug is a "new drug" nor for any right of appeal from any such determination.

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[1] There was an earlier Food and Drug Act of 1906. 34 Stat. 768 (1906). It did not provide for any pre-marketing review of the safety of drugs. The sulfanilamide episode in 1938 prompted the enactment of the Federal Food, Drug and Cosmetic Act of that year to replace the earlier Act and to provide, *inter alia*, for such pre-marketing review of "new drugs". See C. W. Dunn, *Federal Food, Drug and Cosmetic Act—A Statement of Its Legislative Record*, pp. 1316–27 (1938). The fears generated by the thalidomide tragedies gave the impetus for the Amendments of 1962. See Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, 185 at p. 191, n. 45 (1971).

[2] Section 355(a), 21 U.S.C.: The actual approval of a "new drug" under the act is normally processed by the Food and Drug Administration (FDA) in the Department of Health, Education and Welfare (HEW), and the approvals, when granted, are generally referred to as New Drug Approvals (NDAs). FDA, when used herein, refers to the Food and Drug Administration, and NDA is intended to describe an approval by FDA of a "new drug" application under the Act.

[3] Section 321 (p) (1), 21 U.S.C.: See also, *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F. Supp. 443, 445, n. 2: "The statutory definition of the phrase 'new drug' controls this case, regardless of any other meaning attributable to the phrase or to the word 'new' by common understanding or other authority."

[4] Section 355(h), 21 U.S.C.

The FDA sometimes offers to render "informal advice" as to whether it considers a product a "new drug" but it uniformly designates such opinion "advice".[5] Accordingly, the responsibility for determining whether its product is a "new drug", requiring pre-marketing clearance by FDA, rests on the manufacturer, who must act at its peril.[6] If it makes an incorrect determination and seeks to market without FDA clearance a drug meeting the definition of a "new drug", it lays itself open to drastic judicial procedures that may be invoked by FDA, i.e.: The product may be seized in an *in rem* action instituted by the Government;[7] its sale may be enjoined in an action begun by the Government;[8] in addition, the manufacturer may be subjected to criminal action.[9] All these remedies must be prosecuted in the District Court and the role of the Secretary is that of plaintiff or prosecutor. The Act thus establishes two forums for the regulation of drugs: One is administrative and deals with the procedures for securing pre-marketing clearances for the statutorily defined "new drug", with right of appeal from a denial of approval, or withdrawal of a previous approval, to the District Court, later changed to the Court of Appeals; the other is judicial and is intended to make effective and give strength to the requirement that "new drugs" be cleared as safe before marketing by providing the Government with certain potent judicial remedies, *available exclusively in the District Court.*

Under the 1938 Act, a new drug was one "not generally recognized by experts * * * as safe for its intended use." The Amendments added "effectiveness" as well as "safety" to the definition. Simply stated, the change effected by the Amendments was that, whereas prior to the 1962 Amendments a drug which was generally recognized as safe was not a "new drug", the Amendments defined a drug as "new" if it were not generally recognized as both safe *and effective*. Furthermore, they replaced the provision for automatic approvals of applications not disapproved within a fixed time with a requirement of a positive act of approval on the part of FDA.[10] They pro-

[5] 21 C.F.R. 130.39.

[6] Cf. *United States* v. *Dotterweich* (1943) 320 U.S. 277, 281, where, speaking of the Act of 1938, the Court said: "In the interest of the larger good it puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger."

[7] Section 334, 21 U.S.C.

[8] Section 332, 21 U.S.C.

[9] Section 333, 21 U.S.C.

[10] Section 355(c), 21 U.S.C.

ceeded to provide that the Secretary must find as a basis for clearance of a new drug not only safety but "substantial evidence" of effectiveness, "consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectveness of the drug involved." The applicability of these amendments, including the revised definition of "new drug" to drugs already marketed, either under previously issued NDAs, or as "old drugs" requiring no FDA approval, was carefully spelt out in the Amendments and certain "grandfather rights" were granted. For all previously NDA'd drugs, the Amendments conferred a grace period of two years after the effective date of the Amendments within which to prepare evidence to satisfy the new requirement of efficacy added by the revised definition of "new drug"; during that "transitional" period no revocation or withdrawal of approval because of a lack of substantial evidence of efficacy of such drugs was permitted.[11] For a drug, however, which on the day prior to the enactment of the Amendments was (1) being "commercially used or sold in the United States," (2) "was not a new drug as defined by" the pre-Amendment statute and (3) "was not covered by an effective (new drug application, * * *" "on the day immediately preceeding the enactment date" of the Amendments, there was a permanent exemption from the efficacy provisions of the Amendments so long as the drug's labeling remained the same.[12] In summary, these provisions required that, "Those drugs which had obtained effective NDAs must be proven efficacious after two years; those which had not need never be proven efficacious so long as they had become safe prior to the 1962 Amendments." [13]

[11] Section 107(c)(3), P.L. 87-781, Section 321, Supplement 1972, 21 U.S.C.

[12] Section 107(c)(4), P.L. 87-781, Section 321, 1972 Supplement, 21 U.S.C.; see, also, *Tyler Pharmacal Distrib. Inc.* v. *U.S. Dept. of Health, E. & W.* (7th Cir. 1969) 408 F. 2d 95, 99: It should be noted that Section 321(p)(1) provides a "grandfather clause" applicable to pre-1938 drugs. This clause is not relevant to this action, which is concerned with drugs introduced between 1938 and 1962, and the subsequent references to "grandfather clause" in this opinion are to section 107(c)(4).

[13] Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, p. 196 (1971): See, also, *United States* v. *Allan Drug Corp.* (10th Cir. 1966) 357 F. 2d 712, 719, note 9, quoting from the Supplemental Report of the Senate Committee on Drug Amendments of 1962, as set forth in the notes to Section 321, 21 U.S.C.:

"Thirdly, in the case of a drug on the market which was never

The "grandfather clause" set forth in Section 107(c)(4) simply continues for the products satisfying its criteria the pre-1962 definition of a "new drug". Its effect is to assure that a drug which was generally recognized by qualified experts as safe for the purposes recommended for its use on October 9, 1962, need not be NDA'd as *effective* under the new requirements for the issuance of an NDA as a "new drug". But any drug, whether requiring an NDA or not, whether a "new drug" or an "old drug", is subject to the misbranding provisions of the Act and may be proceeded against on that basis. A false claim of either safety or effectiveness constitutes misbranding, rendering a drug subject to both civil and criminal penalties. *United States* v. *Article of Drug Labeled Decholin* (D.C. Mich. 1967) 264 F. Supp. 473, 482–3; *United States* v. *Lanpar Company* (D.C. Tex. 1968) 293 F. Supp. 147, 153–4.[14] Accordingly, in *United States* v. *Guardian Chemical Corporation* (2d Cir. 1969) 410 F. 2d 157, a drug manufacturer was acquitted of a charge of marketing a "new drug" without securing an NDA, but was convicted under a separate count of the indictment charging misbranding. "Thus", as one commentator has aptly stated, "the amplications of the FDA's authority (as granted by the 1962 Amendments) is (was) not due to the absence of power to proceed against ineffective drugs, but rather to authorize the exercise of that power at the initial stage, that is, *before* marketing, and also to shift the burden of proof to the applicant." Jurow, *The Effect on the Pharmaceutical Industry of the "Effectiveness" Provisions of the 1962 Drug Amendments*, 19 Food, Drug, Cosmetic Law Journal, 110, at p. 116 (1964).[15]

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subject to the new-drug procedure before, the amendments to the new drug definition relating to drug effectiveness would not apply to existing labeling claims."

In the Conference Report of the House Managers on the Amendments, it was stated that the Amendments included "the Senate language providing with respect to existing label claims of drugs that have never previously been subject to the new-drug procedure substantially the same savings provisions as the corresponding provision of the House bill (Section 197(d))." *U.S. Code Congressional and Administrative News*, 87th Congress, 2d Session (1962), p. 2932. Again, in H.R. Rep. #2526, p. 23, it is stated that the exemption granted by the "grandfather clause" applies "to existing claims of drugs that have never been subject to the new-drug procedure".

[14] See, also, *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 548: "A good case could certainly be made that, quite apart from this, the 'efficacy' of a drug is necessarily related to the use recommended."

[15] See, also, Senate Report #1744, *U.S. Code Congressional and Administrative News*, 87th Cong., 2d Sess. (1962), pp. 2892 and 2893, where, in

The plaintiffs, manufacturers of a prescription drug containing pentylenetetrazol and nicotinic acid, claim the protection of the "grandfather clause" included in Section 107(c)(4) for their products and that contention represents the substantive issue in this case. It is undisputed that plaintiffs had marketed their product commercially for many years prior to and on October 9, 1962,[16] without an NDA under the claim that it was not a "new drug" within the definition of the Act, and therefore required no NDA. Such claim was supported, it is asserted, both by previous informal advice of the Secretary and by the general recognition of the safety of such product by "experts qualified by scientific training and experience" to make such evaluation. The defendants, the Secretary of HEW and the Commissioner of Food and Drugs, in their brief, concede that "Over the years since 1938" and until 1968, the Food and Drug Administration had given the opinion that certain pentylenetetrazol combinations similar to those of the appellant were not "new drugs."[17] Moreover, the District Court observed in its opinion that there was "no contention (by the FDA) that the use of the plaintiffs' drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs." On this basis, the plaintiffs contended that they met exactly the criteria established for exemption from the requirements of general recognition by qualified experts of the effec-

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justifying the Amendments, it is stated: "* * * where a drug is essentially innocuous, it (FDA) must clear the drug despite the fact that its claim of effectiveness is not borne out by the evidence. In such cases the Food and Drug Administration may proceed against the drug manufacturer by seizure of the drug for misbranding. However, the Department believes that the manufacturer should satisfy the Food and Drug Administration that his product is effective for the purposes claimed before it is marketed. * * * No question of safety is involved, and the Food and Drug Administration presently has ample power, including seizure, to proceed against any safe drug for which unsupported claims of effectiveness are made."

[16] This was the day "immediately preceding the enactment date" of the Amendments of 1962.

[17] It is, of course, axiomatic that such opinions or advice can create no estoppel against the Government. *AMP Incorporated* v. *Gardner* (D.C.N.Y. 1967) 275 F. Supp. 410, 412, n. 1, aff. 389 F. 2d 825, cert. den. 393 U.S. 825, reh. den. 395 U.S. 917. The most that can be claimed for such opinions is that they lend color and good faith to the plaintiffs' claims. FDA not only has the right but is obligated to change its opinion if it learns its prior position was erroneous. *United States* v. *60 28-Capsule Bottles, More or Less, etc.* (D.C.N.J. 1962) 211 F. Supp. 207, 215, aff. 325 F. 2d 513.

tiveness of their products as provided in the permanent grandfather section of the 1962 Amendments.

Prior to the filing of this action, however, the defendants withdrew their advice that products such as those distributed by the plaintiffs were "old drugs" and contended that such products did not qualify for exemption under the "grandfather clause", Section 107(c)(4). The basis for this contention was the claim (1) that these drugs were not generally recognized by qualified experts as safe as of the effective date of the Amendments of 1962 and (2) that they were "me-too" drugs, whose marketability without FDA clearance depended in turn on the NDAs granted the basic drug, and for that reason must be regarded as drugs covered by an effective NDA on the effective date of the Amendments.[18] Faced with this threat, the plaintiffs began this action for a declaratory judgment sustaining their right to exemption from proof of the effectiveness of their product and for injunctive relief awaiting the disposition of their claim for exemption. The defendants directed against the complaint a motion to dismiss or for summary judgment, which, in essence, (1) asserted primary jurisdiction in the Secretary to determine whether the products of the plaintiffs met

[18] The defendants assert that three "new drug" applications filed by other manufacturers and earlier approved by the FDA covered drugs similar in every particular to those marketed by the plaintiffs. Proceedings for withdrawal of the approval of such "new drugs" had been begun by FDA in advance of the filing of this action. In fact, such proceedings to a large extent prompted this action. It is the contention of the defendants that the withdrawal of what they describe as "the primary NDAs" operates to remove the marketability from what they assert are the "me-toos" or non-NDA'd drugs which are similar to other drugs which have secured effective NDAs. The plaintiffs deny that their drugs are like those previously NDA'd. They argue that those NDA'd products, unlike theirs, are intravenously administered or are a compound containing, in addition to the components of plaintiffs' drugs, reserpine. Such changes in formula or method of administering vitiated any claim by their manufacturers that they were marketing an old drug and required an approval as a new drug. The plaintiffs assert their drugs are not subject to any such disability. These, however, are questions of fact not relevant to the simple question of jurisdiction presented by this appeal and may be inquired into on remand. Even if the products of the plaintiffs be deemed "me-too" drugs (i.e., simply "a copy of a pioneer drug which preceded it on the market"), it is by no means clear that they do not "meet the requirements for section 107(c)(4) protection" and the argument of the Government to the contrary has been described as "lacking in merit." See, Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown Law Journal, 185 at pp. 203–207 (1971); Hagan, *Grandfather Protection under the Drug Amendments of 1962*, 19 Food Drug Cosmetic Law Journal, 119, at p. 125 (1964).

the requirements for exemption under Section 107(c)(4), particularly whether they were "new drugs", requiring pre-marketing approval under the Act, (2) denied the propriety of a declaratory judgment action, and (3) claimed that the products of the plaintiffs were "new drugs" which did not qualify for exemption under the "grandfather clause".

The District Court sustained the right of the plaintiffs to maintain a suit for a declaratory judgment and the jurisdiction of the Court in such action to determine judicially whether the products of the plaintiffs were "new drugs", on the effective date of the Amendments, and whether they were or were not entitled to the benefits of the "grandfather clause".[19] However—and this is the nub of the controversy between the parties on this appeal—it concluded that the Secretary had concurrent jurisdiction to determine whether plaintiffs' products were "new drugs", requiring pre-marketing clearance, and that, because of the greater expertise of the Secretary in the field, it deferred to the Secretary's assumed jurisdiction to determine whether the drugs of the plaintiffs came within the exemption provided by the "grandfather clause". It enjoined any action against the plaintiffs and their products until the plaintiffs had been accorded a hearing before the Secretary on the issue of the qualifications of these drugs for protection under the "grandfather clause". It is the conclusion of concurrent jurisdiction in the Secretary and deference to that assumed concurrent jurisdiction from which the plaintiffs have prosecuted this appeal.

The defendants, on the other hand, have not cross-appealed and have accordingly acquiesced in the decision of the District Court that the action is properly maintainable as a declaratory judgment proceeding under Section 2201, 28 U.S.C. and that the District Court has jurisdiction over the substantive issue in this case, i.e., whether plaintiffs' products are "new drugs",

[19] In support of the right of the plaintiffs to maintain a suit for declaratory judgment, the District Court relied on *Abbott Laboratories* v. *Gardner* (1967) 387 U.S. 136 and the companion case of *Toilet Goods Assn.* v. *Gardner* (1967) 387 U.S. 158. Additional support for such right is found in *AMP, Incorporated* v. *Gardner, supra; Durovic* v. *Richardson* (D.C. Ill. 1971) 327 F. Supp. 386; *Lemmon Pharmacal Co.* v. *Richardson* (D.C. Pa. 1970) 319 F. Supp. 375. The right of the Court to determine the applicability of the "grandfather clause" is equally clear and has been sustained in *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F. Supp. 443, 445; and *United States* v. *Article Consisting of 36 Boxes, etc.* (D.C. Del. 1968) 284 F. Supp. 107, 112, n. 13, aff. 415 F. 2d 369.

as defined in the Act. The question in the case is thus whether the Secretary has concurrent jurisdiction to determine whether a drug is a "new drug" under the Act or whether that issue is cognizable only in the District Court. Contrary to the conclusion of the District Court, we conclude that the Act confers no such jurisdiction on the Secretary and, therefore, no basis for any deference by that Court to the concurrent jurisdiction of the Secretary.

The FDA has neither primary jurisdiction, as the defendants argue, nor concurrent jurisdiction, as the District Court concluded, to adjudicate whether a product is an old or a new drug. It may, in its prosecutorial role, reach a conclusion that a product being marketed is a "new drug" requiring premarketing approval; but that opinion is not adjudicatory, it is only the basis on which the FDA, as the prosecutor or initiator or either a seizure or injunctive action in the District Court, may invoke the jurisdiction of that Court to determine, among other issues, whether the drug challenged is a "new drug". There is manifestly no provision in the Act for an administrative proceeding before the Secretary to compel the filing of a "new drug" application or to halt the marketing of a drug for which there is no approval by the Secretary.

It is not without significance that, so far as the official reports reflect, the Secretary has never attempted directly to exercise such jurisdiction. The only occasions on which he has sought to assert such jurisdiction has been as an element in his defense to a declaratory judgment action.[20] Moreover, when FDA undertook its new responsibilities under 1962 Amendments, it sought merely to review "the efficacy of *all new drugs that had been cleared*, for safety only, between 1938 and October 10, 1962"[21] (Italics added) and enlisted the services of the National Academy of Sciences-National Research Council for this limited task. It did not assert the right to review, or assume the burden of reviewing, for efficacy, drugs such as those involved here, which had been commercially marketed on the basis of a general recognition of safety without an effective NDA as of the effective date of the 1962 Amendments. It, thus, recognized that its adjudicatory rights extended merely to the

[20] See, *Hynson, Westcott & Dunning, Inc.* v. *Richardson* (Civ. No. 2112, D. Md., decided 9/16/70); and *Ciba Corp.* v. *Richardson* (Civ. No. 1210-70, D.N.J., decided 3/10/71); but cf., *Lemmon Pharacal*, *supra*.

[21] See *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 539, and 31 F.R. 9426.

approval, or the withdrawal of approval,[22] of a drug embraced in a "new drug" application that had been approved. This confirms the conclusion that the halting of the marketing of a drug, for which there is no NDA, may not be by administrative action but must be by an injunction or *in rem* seizure proceeding, in which the Secretary appears, not in a judicial but in a prosecutorial role.[23] Those are the procedures prescribed and available to the Government under the Act.[24] The Secretary, it is true, has offered to provide "advice" on whether a product meets the qualification of an old drug but he categorizes his action in such instances as merely "advice" and makes no claim of finality therefor. Nor is there, as we have already observed, any provision for judicial review of such "advice".[25] The only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of an approval, of a "new drug" application.[26] That this is so follows from the limitations placed by the Act on judicial review of the decisions of the Secretary. The Secretary himself asserted, shortly after the enactment of the 1962 Amendments, in *Turkel* v. *Food and Drug Administration, Dept. of H.E.W., supra,* at p. 845, that the Act "grants a right to appeal only from an order of the Food and Drug Administration approving or disapproving a New Drug Application". In keeping with the Secretary's contention as to the extent of his adjudicatory powers, the Court in that case held that the right of appeal from an order of the Secretary "applies only to an order of the Secretary refusing or withdrawing approval of an application for sale and

[22] The authority of the Secretary to withdraw an approval of any "new drug" application filed under the Act of 1938 after hearing is specifically granted by Section 355(e), 21 U.S.C.

[23] Of course, in a proper case the Government may also institute criminal proceedings in the District Court. See Section 333, 21 U.S.C.

[24] Cf. *United States* v. *Allan Drug Corporation* (10th Cir. 1966) 357 F. 2d 713, 718, cert. den. 385 U.S. 899, in which the Secretary is quoted to the effect that, " 'As to drugs already on the market that have never been subject to the new-drug procedure but are not generally recognized as effective, the burden remains on the Government to prove *in court*, insofar as unchanged labeling claims are concerned, they do not have their claimed effect. If the labeling claims are changed, however, these must be approved under the new-drug procedure.' " (Italics added.)

[25] See *Turkey* v. *Food and Drug Administration, Dept. of H.E.W.* (6th Cir. 1964) 334 F. 2d 844, 846, cert. denied 379 U.S. 900, rehearing denied 380 U.S. 927: "The jurisdiction of the United States Courts of Appeal to review administrative acts of federal agencies is wholly dependent upon statute."

[26] Section 355(b), 21 U.S.C.

distribution of a new drug" (at pp. 845–6). It is not to be assumed that the Act confers an adjudicatory right on the Secretary from which no judicial review, however limited, is provided or allowed. Yet this is the unusual situation that would be presented if the Secretary were held to have jurisdiction to adjudicate whether a drug meets the statutory criteria of a "new drug".[27]

The District Court, in finding concurrent jurisdiction, held that "This grant of authority to approve or withhold approval of new drug application, * * * necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which required an approved new drug application for lawful interstate shipment." This reasoning assumes that an application for approval by the Secretary under the Act poses as its initial issue whether the product is a new drug. No such issue is posed by the application. The very filing of the application is a concession and recognition by the applicant-manufacturer that the article is a "new drug"; otherwise, there would be no reason to file the application. As a matter of fact, in the prescribed form of application, the applicant describes his product as a "new drug". 21 C.F.R. 130.4. The applicant makes the determination whether his product is a "new drug" and whether he must file for pre-marketing clearance by the Secretary. And when filed, the application puts in issue only one question: Is the article safe and effectice? That and that alone is the issue to be considered by the Secretary in connection with an application for approval filed by a manufacturer under Section 355(d), 21 U.S.C. That issue is quite different from that presented when there is an issue whether a drug fits the statutory defination of "new drug" in the Act.

The criterion for ascertaining whether a product is within statutory definition of "new drug" under the Act is not safety and effectiveness *per se*, which as we have observed, is the issue before the Secretary in connection with application for approval of a "new drug", but "whether the government has shown by a preponderance of the evidence that the drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectivness of drugs, as safe and effective for use under the conditions pre-

[27] Cf., *Abbott Laboratories* v. *Gardner* (1967) 387 U.S. 136, at p. 140.

scribed, recommended or suggested in the labeling thereof." [28] That is an issue that must be and is resolved, sometimes with, and at other times without a jury, in practically every injunctive, seizure, or criminal proceeding under the Act. See, for instance, *United States* v. *Articles of Drug Labeled "Quick-O-Ver", supra; United States* v. *41 Cases, More or Less* (5th Cir. 1970) 420 F. 2d 1126, 1128; *United States* v. *Article of Drug, etc., supra,* at p. 392; *United States* v. *Article . . . Consist. of 216 Carton* (2d Cir. 1969) 409 F. 2d 734, 742; *United States Article Consisting of 36 Boxes, etc., supra,* at p. 113; see, also, *United States* v. *Article of Drug, etc.* (D.C. Md. 1971) 331 F. Supp. 912, 915–7. That was one of the issues resolved in the declaratory action of *Lemmon Pharmacal Co.* v. *Richardson, supra.*[29] It is manifestly a justiciable issue and the plaintiffs are entitled to a judgment on that issue by the Court, which alone has the jurisdiction to resolve it. In the absence of any statutory review proceedings within which they may assert their claim of exemption, the plaintiffs are not to be compelled to proceed at their peril, subject to the possibility of both civil and criminal penalties, but are entitled to seek relief by way of a declaratory judgment action. The District Court should accordingly have retained jurisdiction and proceeded to determine whether the plaintiffs' drugs met the criteria for exemption under Section 107(c)(4). We deem it premature for us to consider at this stage whether plaintiffs' products meet such criteria. That issue was not developed in the record before, or ruled on by, the District Court.[30] Upon remand, the issue

[28] *United States* v. *Articles of Drug Labeled "Quick-O-ver", supra,* at pp. 445–6.

See, also: *AMP, Incorporated* v. *Gardner, supra,* at p. 831: "But the safety of the products is not what is at issue here. The question is whether there is general recognition among qualified experts of the products' safety and effectiveness—if there is not, the products must be submitted to the Secretary of Health, Education, and Welfare for a determination as to safety, adequacy of testing, etc."

United States v. *Article of Drug, etc.* (5th Cir. 1969) 415 F. 2d 390, 392: "Both sides agree that the nature of expert opinion about Furestrol, and not its actual safety or effectiveness, is the ultimate fact issue."

Cf., *United States* v. *Seven Cartons, More or Less, etc.* (7th Cir. 1970) 424 F. 2d 1361, 1365.

[29] In discussing this case, the commentator in 60 Georgetown Law Journal, p. 199, note 87, says: "In *Lemmon Pharmacal,* the Court, while noting that determining safety and efficacy would normally be within the primary jurisdiction of the agency, concluded that the question of section 107(c)(4) protection was properly before it."

[30] See *United States* v. *Article Consisting of 36 Boxes etc., supra,* at p. 113.

can be considered by the Court in the light of the record that may be made by the parties.

Remanded with directions.

[*Filed, May 23, 1972, Samuel W. Phillips, clerk.*]

In the United States Court of Appeals for the Fourth Circuit

No. 71-1243

BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., ET AL., APPELLANTS

v.

ELLIOT P. RICHARDSON, SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, APPELLEES

Appeal from the United States District Court for the District of South Carolina.

Judgment

This cause came on to be heard on the record from the United States District Court for the District of South Carolina, and was argued by counsel.

On consideration whereof, It is now here ordered and adjudged by this Court that the judgment of the said District Court appealed from, in this cause, be, and the same is hereby, reversed. The case is remanded to the United States District Court for the District of South Carolina, at Greenville, with directions consistent with the opinion of this Court filed herewith.

SAMUEL W. PHILLIPS,
Clerk.

Supreme Court of the United States

No. 72–555

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, ET AL., PETITIONERS

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

Order allowing certiorari. Filed January 8, 1973.

The petition herein for a writ of certiorari to the United States Court of Appeals for the Fourth Circuit is granted. The case is consolidated with Nos. 72–394, 72–414, 72–528 and 72–666, and a total of three hours is allotted for oral argument.

United States Court of Appeals for the Fourth Circuit

Civil No. 71–1596

USV PHARMACEUTICAL CORPORATION, APPELLANT

v.

ELLIOT L. RICHARDSON, ET AL., APPELLEES

RELEVANT DOCKET ENTRIES

Date	
6/29/71	Record on appeal in three volumes (Volumes I, II, and III) filed and appeal docketed.
6/29/71	Exhibits in one volume (Volume IV) received from the Clerk of the District Court at Alexandria, Virginia.
6/29/71	Deposition of Theodore H. Spaet in one volume (Volume V) received from the Clerk of the District Court at Alexandria, Virginia.
6/29/71	Transcript of proceedings of December 1, 1969 in one volume (Volume VI) filed.
6/29/71	Transcript of proceedings of October 19, and 20, 1970 in one volume (Volume VII) filed.
6/29/71	Transcript of proceedings of October 23, 1970 in one volume (Volume VIII) filed.
6/29/71	Transcript of proceedings of October 26, 1970 in one volume (Volume IX) filed.
6/29/71	Transcript of proceedings of May 4, 1971 in one volume (Volume X) filed.
7/ 6/71	Appearance for the appellee filed and entered.
7/ 6/71	Appearance for the appellants filed and entered.
7/14/71	Appellant's motion for extension of time to file brief and appendix to September 10, 1971, filed. Motion granted.
7/14/71	Appearance for the appellants filed and entered.
8/ 9/71	Appellant's Statement of Issues and Designation of Contents of Record to be included in appendix, filed.
9/10/71	Motion for extension of time of the appellants to September 20, 1971, filed. Motion granted.
9/27/71	Brief for appellants filed. 25 copies.
9/27/71	Joint appendix filed. 10 copies.
10/ 7/71	Appellee's motion for extension of time to file brief filed. Motion denied.
10/12/71	Order extending the time to file appellee's brief to November 22, 1971, filed.
11/16/71	Notice of oral argument mailed to Moncure, Hoffman, Hutt, and Epstein.
11/24/71	Brief and appendix for appellees filed. 25 copies.
12/ 6/71	Reply brief for appellants filed. 25 copies.
12/ 8/71	Cause argued before Winter, Russell, Field, Circuit Judges, and Submitted.

12/17/71 Above record on appeal with tape mailed to Judge Russell.

5/12/72 Record on appeal in nine volumes received from Judge Russell.

5/24/72 Opinion filed.

5/24/72 Opinion and Clerk's Memorandum mailed to counsel of record. (Mailed to Epstein, Hoffman, and Moncure.) Copy of opinion mailed to the Clerk of the district court at Alexandria, Virginia.

5/24/72 Judgment of the district court reversed. Judgment filed.

6/ 1/72 Appellant's verified bill of costs, filed.

6/ 9/72 Motion for leave to file petition for rehearing out of time to June 9, 1972, filed. Motion granted.

6/ 9/72 Petition for rehearing, filed.

7/ 5/72 Order denying appellee's petition for rehearing and suggestion for rehearing en banc, filed.

7/13/72 Certified copy of the judgment and printed copy of the opinion transmitted to the Clerk of the District Court at Alexandria, Virginia.

7/13/72 Record on appeal in three volumes (Vols. I, II and III), exhibits in one volume (Vol. IV), deposition of Theodore H. Spaet in one volume (Vol. V), transcript of proceedings of December 1, 1969 in one volume (Vol. VI), transcript of proceedings of October 19 and 20, 1970 in one volume (Vol. VII), transcript of proceedings of October 23, 1970 in one volume (Vol.. VIII), transcript of proceedings of October 26, 1970 in one volume (Vol. IX and transcript of proceedings of May 4, 1971 in one volume (Vol. X) returned to the Clerk of the District Court at Alexandria, Virginia.

11/ 3/72 Notice evidencing the filing petition for writ of certiorari in the Supreme Court October 30, 1972 filed. (No. 72-666).

1/12/73 Certified copy of order of the Supreme Court granting certiorari January 8, 1973 filed.

7/13/72 Record on appeal in three volumes (Vols. I, II and III), exhibits in one volume (Vol. IV), deposition of Theodore H. Spaet in one volume (Vol. V), transcript of proceedings of December 1, 1969 in one volume (Vol. VI), transcript of proceedings of October 19th and 20th, 1970 in one volume (Vol. VII), transcript of proceedings of October 23, 1970 in one volume (Vol. VIII), transcript of proceedings of October 26, 1970 in one volume (Vol. IX IX) and transcript of proceedings of May 4, 1971 in one volume (Vol. X) received from the Clerk of the District Court at Alexandria, Virginia.

2/ 2/73 Certified record in ten volumes and exhibits in one envelope transmitted to the Clerk of the Supreme Court.

In the United States District Court for the Eastern District of Virginia

Civil Action No. 4915–A

USV PHARMACEUTICAL CORPORATION, 800 SECOND AVENUE, NEW YORK, NEW YORK 10017, PLAINTIFF

v.

WILBUR J. COHEN, SECRETARY OF HEALTH, EDUCATION AND WELFARE, DEPARTMENT OF HEALTH, EDUCATION & WELFARE, WASHINGTON, D.C. 20201, AND HERBERT L. LEY, JR., COMMISSIONER OF FOOD AND DRUGS, FOOD & DRUG ADMINISTRATION, 2221 JEFFERSON DAVIS HIGHWAY, ARLINGTON, VIRGINIA, DEFENDANTS

Complaint for Declaratory Judgment

Plaintiff, by its attorneys, brings this civil action and complains and alleges as follows:

JURISDICTION AND VENUE

1. This action arises under the Federal Food, Drug & Cosmetic Act (hereafter "the Act") 52 Stat. 1040 (1938), as amended, 21 U.S.C. § 301 *et seq.*, and the Drug Amendments Act of 1962 (hereinafter "1962 Amendments") 76 Stat. 789 (1962). Plaintiff seeks a declaratory judgment that certain of its drug products are not "new drugs" within the meaning of the Act, and that the 1962 Amendments do not apply to those products. There exists between the parties an actual controversy on this issue, justiciable in nature, as to which plaintiff requires a declaration of its rights by this Court. The jurisdiction of this Court is conferred by 28 U.S.C. §§ 1337 and 2201.

2. Defendant Herbert L. Ley, Jr., resides in the Eastern District of Virginia.

PARTIES

3. Plaintiff is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business in the State of New York. It manufactures and sells drugs in interstate commerce.

4. Defendant Wilbur J. Cohen is the Secretary of Health, Education and Welfare and is charged by law with the administration of the Act. Defendant Cohen and his predecessors in office will hereafter be referred to as "the Secretary."

5. Defendant Herbert L. Ley, Jr., is the Commissioner of Food and Drugs. He is the head of the Food & Drug Administration, a constituent part of the Department of Health, Education and Welfare. He has been delegated the authority of the Secretary to administer the Act. Defendant Ley and his predecessors in office will hereafter be referred to as "the Commissioner."

NATURE OF THE CONTROVERSY

6. Plaintiff has from time to time manufactured and sold a variety of products containing citrus bioflavonoid compound (hereafter "bioflavonoids"). These products are the subject-matter of this controversy. Plaintiff presently manufactures and sells the C.V.P. line of products (C.V.P. Capsules, C.V.P. Syrup, C.V.P. With Vitamin K Tablets, C.V.P. With Vitamin K Syrup, Duo-C.V.P. Capsules, and Duo-C.V.P. With Vitamin K Tablets). The conditions of use now represented in the labeling of the C.V.P. products are, in substance, the prevention and treatment of abnormal capillary permeability and fragility, and resultant bleeding when they occur in conditions such as gingival bleeding, habitual abortion, threatened abortion, and nonthrombocytopenic purpura. Prior to 1968, plaintiff also manufactured and sold a bioflavonoid product called Bivam; prior to February 1965, a bioflavonoid product called Prednis-C.V.P.; and prior to May 1961, a bioflavonoid product called Prednyl. Bivam, Prednyl and Prednis-C.V.P. are not now manufactured or sold by plaintiff. They contained the same citrus bioflavonoid compound contained in the C.V.P. line of products.

7. Section 505(a) of the Act (21 U.S.C. § 355(a)) provides that

> "no person shall introduce or deliver into interstate commerce any new drug, unless approval of a [new drug] application * * * is effective with respect to such drug."

Until October 10, 1962, the term "new drug" was defined by Section 201(p) of the Act (21 U.S.C. § 321(p)) to mean

> "any drug the composition of which is such that such drug is *not generally recognized,* among experts qualified by scientific training and experience to evaluate the safety of drugs, *as safe* for use under the conditions prescribed, recommended, or suggested in the labeling thereof, * * * [or] which has not * * * been [commercially] used to a material extent or for a material time under such conditions" (emphasis added).

The 1962 Amendments (76 Stat. 796), which became effective October 10, 1962, added the criterion of efficacy to the section 201(p) definition, so as to redefine the term "new drug" to mean

> "any drug the composition of which is such that such drug is *not generally recognized,* among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, *as safe and effective* for use under the conditions prescribed, recommended or suggested in the labeling thereof, * * * [or] which has not * * * been [commercially] used to a material extent or for a material time under such conditions" (emphasis added).

"Grandfather" protection was provided, however, for certain drugs marketed prior to the effective date of the amendments. Section 107(c)(4) of the 1962 Amendments (76 Stat. 789) provides that the new efficacy criterion does not apply

> "in the case of any drug which, on * * * [October 9, 1962] (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the * * * [Federal Food, Drug and Cosmetic] Act as then in force, and (C) was not covered by an effective [new drug] application * * * when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day."

The controversy between plaintiff and defendants is whether plaintiff's bioflavonoid products are entitled to the grandfather protection conferred by Section 107(c)(4).

8. On April 22, 1955, plaintiff filed a new drug application for C.V.P. Capsules, C.V.P. Syrup, and C.V.P. With Vitamin K Syrup. This NDA was designated as NDA 9965, and became effective November 8, 1955. A supplement to NDA 9965 for C.V.P. with Vitamin K Tablets became effective January 19, 1956. A supplement to NDA 9965 for Duo-C.V.P. Capsules became effective May 14, 1956. A new drug application for Prednyl was filed April 3, 1958, designated as NDA 11474, and became effective August 26, 1958. A new drug application for Prednis-C.V.P. was filed April 3, 1958, designated as NDA 11475, and became effective about the same time as NDA 11474. No new drug application or supplement for Duo-C.V.P. With Vitamin K Capsules or for Bivam Tablets was ever filed by plaintiff.

9. On or before October 9, 1962, each of plaintiff's bioflavonoid products was "generally recognized * * * as safe" within the meaning of section 201(p) of the Act; that is, was generally recognized among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended or suggested in the labeling thereof, and had been used to a material extent and for a material time under such conditions otherwise than in investigations to determine its safety for use under such conditions. This was conceded by FDA in correspondence with plaintiff:

(a) On December 12, 1956, believing that its bioflavonoid product Bivam Tablets was "generally recognized * * * as safe," plaintiff wrote a letter to the Food & Drug Administration requesting confirmation that Bivam Tablets was not a new drug. The Food & Drug Administration replied on January 3, 1957, stating that "we do not regard preparations of this composition as new drugs * * *."

(b) On February 28, 1961, believing them to be "generally recognized * * * as safe," plaintiff wrote a letter to the Food & Drug Administration asking whether the products on which, *inter alia*, NDA 9965, NDA 11474, and NDA 11475 had been filed, were "still considered to be 'new drugs'." The Food & Drug Administration replied on April 19, 1961, stating that Prednyl (NDA 11474) and Prednis-C.V.P. (NDA 11475) "are not new drugs when distributed under the labeling provided for in the respective effective new drug applications." In its letter the Food & Drug Administration declined to answer plaintiff's ques-

tion with respect to, *inter alia*, the C.V.P. products (NDA 9965), although the bioflavonoid ingredient therein is the same as in Prednyl and Prednis-C.V.P., and suggested that plaintiff "furnish some information on marketing experience" as well as copies of "labels and labeling." On May 16, 1961, plaintiff responded, enclosing labels and labeling for C.V.P. Capsules, C.V.P. Syrup, C.V.P. With Vitamin K Tablets, C.V.P. With Vitamin K Syrup, Duo-C.V.P. Capsules, and Duo-C.V.P. With Vitamin K Capsules, and stating "it is our recollection that the C.V.P. class of products were no longer considered to be new drugs a short time after the N.D.A. became effective." The Food and Drug Administration did not reply to plaintiff's letter.

10. On May 28, 1968, the Commissioner published in the Federal Register a "Statement of Policy" stating that "all opinions previously given by the Food & Drug Administration to the effect that an article is 'not a new drug' or is 'no longer a new drug' are hereby revoked." The purpose of this "Statement of Policy" was to remove an impediment to later contentions that drugs for which new drug applications had become effective on or before October 9, 1962, were, although generally recognized as safe on that date, subject to section 201(p) as amended by the 1962 Amendments.

11. Section 505(e) of the Act, as amended by the 1962 Amendments, authorizes the Secretary to withdraw approval of a new drug application if he finds

> "on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the *effect* it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; * * * " (emphasis added).

The May 28, 1968, "Statement of Policy" revoking all previous "not-new" opinions recited that the revocation of previous opinions was "of special importance by reason of proposed actions to withdraw approval of new-drug applications for lack of substantial evidence of effectiveness * * * for example, see the notice published in the Federal Register of January 23, 1968 (33 F.R. 818)."

12. The January 23, 1968, notice stated that "the Food & Drug Administration * * * has concluded * * * that there

is no evidence that * * * bioflavonoids are effective for use in man for any condition"; that the Commissioner "intends to publish a notice of opportunity for a hearing on a proposal to withdraw approval of all new-drug applications for drugs containing * * * bioflavonoids" on the ground, added to the Act in 1962 as alleged above, of no substantial evidence of efficacy; and inviting "all holders of new-drug applications" for bioflavonoid products to a meeting for discussion of procedural matters and for the identification and resolution of "problems that may be anticipated as a result of the actions to be taken." The Commissioner further stated in this Federal Register notice that "promulgation of an order withdrawing approval of * * * new-drug applications [for bioflavonoid products] will classify drugs containing any of these components as new drugs for which an approved new-drug application is not in effect" and that "any such drugs then on the market would be subject to regulatory proceedings."

13. On July 10, 1968, pursuant to the intent stated in his notice of January 23, 1968, the Commissioner published in the Federal Register a notice that he proposed to issue an order under Section 505(e) of the Act, withdrawing approval of, *inter alia*, NDA 9965, NDA 11474, and NDA 11475, on the grounds "that there is a lack of substantial evidence that * * * any bioflavonoid has the effect which the drugs purport to have * * * or that such articles * * * are effective for use in man for any condition." The notice stated that "publication of the proposed order will cause any drug for human use containing any * * * bioflavonoid to be a new drug for which an approved new-drug application is not in effect" and that "any such drug then on the market would be subject to regulatory proceedings." Implicit in this notice is the contention that these products are "new drugs" within the meaning of Section 201(p) of the 1962 Amendments and that the grandfather protection of Section 107(c)(4) does not apply.

14. In fact, each of plaintiff's bioflavonoid products satisfied the conditions of Section 107(c)(4) necessary to qualify for grandfather protection; the amended section 201(p) of the Act therefore does not apply. On October 9, 1962, each of plaintiff's bioflavonoid products for which a new drug application had previously been filed and had become effective was "generally recognized * * * as safe" within the meaning of section 201(p) of the Act; therefore was not a new drug as defined thereby; and

therefore was no longer "*covered* by an effective new drug application." On October 9, 1962, Duo-C.V.P. With Vitamin K Capsules and Bivam Tablets were "generally recognized * * * as safe" within the meaning of section 201(p) of the Act; therefore were not new drugs as defined thereby; and had never been covered by an effective new drug application. All of plaintiff's bioflavonoid products, with the exception of Prednyl which was discontinued in May 1961, were commercially used or sold in the United States on October 9, 1962.

15. There is an actual controversy, justifiable in character, between plaintiff and defendants as to whether the 1962 Amendments to the definition of the term "new drug" in section 201(p) of the Act apply to plaintiff's bioflavonoid products. Plaintiff has taken the position that the efficacy provisions do not so apply. Defendants have taken the final position that they do; assert that these products are covered by effective NDA's; have instituted, and continue to maintain, administrative proceedings against plaintiff to withdraw approval of the NDA's based upon an alleged lack of substantial evidence of efficacy; and threaten to institute or cause to be instituted other regulatory proceedings against plaintiff on the same basis.

16. The existence of the following controversy requires plaintiff, in order to avoid the threat of criminal prosecution, seizures of its products, and injunction actions, to comply with burdensome administrative regulations, except insofar as compliance therewith may be waived by defendants. Plaintiff will further be required, in order to avoid such threat, to withdraw its bioflavonoid products from the market if approval of its bioflavonoid new-drug applications should be withdrawn by the Commissioner at the conclusion of the pending administrative proceedings. The institution of enforcement actions would in itself severely injure plaintiff in its ability to market its bioflavonoid products. The controversy between plaintiff and defendants cannot be resolved in any pending or future administrative proceeding, but, unless the declaratory judgment prayed herein is granted, can be resolved only in criminal prosecutions, injunction actions or proceedings for seizure and condemnation of the products involved.

Wherefore, plaintiff prays that this Court enter its judgment declaring that plaintiff's bioflavonoid products are not "new drugs" within the meaning of the Federal Food, Drug & Cosmetic Act as amended, and that the efficacy provisions of the

Drug Amendment Act of 1962 do not apply to those products; and plaintiff further prays for such other and further relief as may be just and proper.

ROBERT L. WALD,
CARLETON A. HARKRADER,
SELMA M. LEVINE,
JOEL E. HOFFMAN,
Wald, Harkrader & Rockefeller,
1225 Nineteenth Street, N.W.,
Washington, D.C. 20036
THOMAS MONCURE,
121 South Royal Street,
Alexandria, Virginia 22313.
Attorneys for Plaintiff.

Dated: AUGUST 6, 1968.

In the United States District Court For the Eastern District of Virginia

[Caption Omitted]

Answer

Defendants, by the United States Attorney for this District, for Answer to the Complaint, say:

1. With respect to the allegations in paragraph 1 of the Complaint, Defendants admit that this Court has jurisdiction, but deny that there exists an actual controversy, justicable in nature; assert that this is not a proper case for the Court's exercise of its discretion under the Declaratory Judgments Act (28 U.S.C. 2201); and assert that the Drug Amendments of 1962, PL. 87–781, do, in fact, apply to Plaintiff's products, which are "new drugs" within the meaning of the Federal Food, Drug, and Cosmetic Act.

2. Defendants deny the allegations of paragraph 2 of the Complaint and assert that the official residence of Herbert L. Ley, Jr., M.D., Commissioner of Food and Drugs, is Washington, D.C.

3. Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 3 of the Complaint.

4. Defendants admit the allegations of paragraph 4 of the Complaint.

5. Defendants admit the allegations of paragraph 5 of the Complaint.

6. Defendants are without knowledge or information sufficient to form a belief as to the truth of the allegations of paragraph 6 of the Complaint.

7. Defendants admit the allegations of paragraph 7 of the Complaint, except for the last sentence, which is denied.

8. Defendants admit the allegations of paragraph 8 of the Complaint.

9. With respect to paragraph 9 of the Complaint, Defendants deny the allegations preceding subparts (a) and (b); admit the allegations of subparts (a) and (b), except that Defendants are without knowledge or information sufficient to form a belief as to the allegation in subpart (b) that the bioflavonoid ingredient in the C.V.P. products (NDA 9965) is the same as in Prednyl and Prednis-C.V.P.

10. Defendants admit the allegations of the first sentence and deny the allegations of the second sentence of paragraph 10 of the Complaint

11. Defendants admit the allegations in paragraph 11 of the Complaint.

12. Defendants admit the allegations of paragraph 12 of the Complaint.

13. Defendants admit the allegations of paragraph 13 of the Complaint, except for the last sentence thereof, which is denied.

14. Defendants deny the allegations of paragraph 14 of the Complaint and assert that Plaintiff's products other than Prednyl were commercially used or sold in the United States on October 9, 1962; that the products are not entitled to grandfather protection because the drugs were, on October 9, 1962, new drugs as then defined by Section 201(p) of the Federal Food, Drug, and Cosmetic Act; and/or were covered by effective new drug applications under Section 505 of the Act.

15. Defendants deny the allegations of paragraph 15 of the Complaint, except that Defendants admit taking the position that Plaintiff's products listed in the Notice of Opportunity for Hearing dated July 10, 1968, 33 F.R. 9908, are subject to the efficacy provisions of the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act (Section 201(p)) and that such drugs are covered by effective new drug applications.

16. With respect to the allegations of paragraph 16 of the Complaint, Defendants deny that Plaintiff is threatened by any criminal prosecutions, seizures of its products, or injunction actions, on the basis of the Notice of Opportunity for Hearing dated July 10, 1968, 33 F.R. 9908; and deny that the administrative regulations are burdensome. Defendants assert that Plaintiff has elected to avail itself of the opportunity for hearing on the proposed order to withdraw approval of its new drug applications and assert that, until Plaintiff has fully exhausted its administrative remedies, including review by a United States Court of Appeals upon a timely petition, and by the United States Supreme Court upon certiorari or certification, there is no case or controversy before the Court. Defendants admit that Plaintiff would be required to remove its bioflavonoid drugs from the market but only if the final order of the Commissioner, after hearing, withdraws approval of Plaintiff's bioflavonoid new drug applications and if the Commissioner's order is sustained after judicial review under the Act, but assert that the terms of any such order are speculative at this time. Defendants deny all other allegations contained in paragraph 16.

First Affirmative Defense

Venue is improperly laid before this Court.

Second Affirmative Defense

There is no controversy, justiciable in nature; Plaintiff is simply party to a hearing on a proposed order to withdraw approval of its new drug applications and has not exhausted its administrative remedies.

Third Affirmative Defense

The new drug provisions of the Federal Food, Drug, and Cosmetic Act apply to Plaintiff's products. Plaintiff's products are not entitled to grandfather protection under Section 107(c)(4) of the Drug Amendments of 1962, P.L. 87–781, inasmuch as: (1) Prednyl was not commercially used or sold in the United States on October 9, 1962; (2) Plaintiff's products were new drugs as of that date and as then defined by law; and/or (3) Plaintiff's products were covered by effective new drug applications on that date. Plaintiff makes no showing that the third condition of the grandfather section was met: even if Plaintiff's products met the second condition of not being new drugs as of October 9, 1962, they were covered by effective new drug appli-

cations within the meaning of Section 107(c)(4) of the 1962 Amendments. The Notice of Opportunity for Hearing is entirely in accordance with provisions of the Federal Food, Drug, and Cosmetic Act.

Fourth Affirmative Defense

There is a complete want of equity in the Plaintiff's complaint which should persuade this Court not to exercise discretionary jurisdiction under the Declaratory Judgments Act in that the Plaintiff has been, and seeks to continue, marketing a number of drugs with claims that the drugs will be effective in treating abnormal capillary permeability and fragility (hemorrhagic states), which claims have been and are being made to promote the sale of the drugs despite the Plaintiff's own knowledge derived from a comprehensive review of the medical literature, and despite the report of an independent review conducted by a panel of experts of the National Academy of Sciences-National Council-Drug Effectiveness Study, that there is no substantial evidence that the drugs will have the effectiveness claimed for them and indeed that there is no substantial evidence that the drugs will be effective for any use in man, and it thus would be inequitable for this Court to lend its assistance to the continued marketing of these worthless drugs intended to be sold to the public for medical uses wholly unsupported by substantial medical evidence.

Wherefore, having fully answered the Defendants pray:

1. That the relief requested by the Plaintiff be denied and that the action be dismissed; and

2. That the Defendants be given all such other and further relief as to the Court may seem just and proper.

_____,
United States Attorney.

_____,
Assistant United States Attorney.

Certificate of Service

I hereby certify that a copy of the foregoing Motion for Correction of Sentence was mailed, postage pre-paid, to Joel E. Hoffman, Esquire, Wald, Harkrader & Rockefeller, 1225 Nineteenth Street, N.W., Washington, D.C., 20036, this 25th day of October.

JOHN D. SCHMIDTLEIN,
Assistant United States Attorney.

In the United States District Court for the Eastern District of Virginia

[Caption Omitted]

Motion to Dismiss

Defendants, the Secretary of Health, Education, and Welfare, and the Commissioner of Food and Drugs, by their attorneys, move to dismiss this case for the following reasons and on the following grounds:

1. On October 17, 1970, there was published in the Federal Register an order withdrawing approval of the following new drug applications:

NDA No.	Drug Name	Applicants Name and Address
6-065	C.V.P.; C.V.P. w/Vitamin K; Bivan Tablets; Duo-C.V.P. w/Vitamin K Capsules	U.S. Vitamin Corp., 26 Vark Street, Yonkers, New York, 10701
11-474	Prednyl Tablets	Arlington-Funk Labs., Division of U.S. Vitamin Corp., 26 Vark St., Yonkers, N.Y. 10701
11-475	Prednis C.V.P. Capsules	Arlington-Funk Labs.

2. The above listed drugs are the subject matter of this action.

3. The Federal Food Drug and Cosmetic Act, 21 U.S.C. 355(h), provides that when an order is entered by the defendants withdrawing approval of any new drug application, appeal is to the United States Court of Appeals for the circuit wherein the applicant resides or has his principal place of business or in the United States Court of Appeals for the District of Columbia Circuit. There is no appeal to any United States District Court.

4. A final order having been entered withdrawing approval of the new drug applications which cover the drugs which are the subject matter of this action, this Court has no jurisdiction and this case must be dismissed for lack of jurisdiction.

———,
United States Attorney.

———,
Assistant United States Attorney.

Certificate of Service

I hereby certify that on this 19th day of October 1970 I served a copy of the foregoing Motion to Dismiss and Points and Authorities in Support of said Motion by mailing same, postage prepaid to Thomas Moncure, Esquire, 121 South Royal Street, Alexandria, Virginia 22314.

HOWARD S. EPSTEIN,
Attorney, Department of Justice.

In the United States District Court for the Eastern District of Virginia

[Caption Omitted]

Motion for Clarification of Order and Memorandum Opinion

Plaintiff USV Pharmaceutical Corp. respectfully requests the Court's guidance in interpreting the order and memorandum opinion filed herein on April 1, 1971. Specifically, we ask the Court to confirm that in its order and opinion the Court has found:

1. That plaintiff's bioflavonoid products here in question are, today, not "new drugs" under the pre-1962 statutory definition of the term, and therefore exempt from the "new drug" provisions of the statute.

2. That on October 9, 1962 plaintiff's bioflavonoids were, and are today, generally recognized by qualified experts as safe for their intended uses, as the word "safe" was then understood.

Respectfully submitted,

THOMAS MONCURE,
121 South Roy Street,
Alexandria, Virginia 22314.
SELMA M. LEVINE,
JOEL E. HOFFMAN,
Wald, Harkrader, Nicholson & Ross,
1320 Nineteenth Street, N.W.,
Washington, D.C. 20036.

APRIL 12, 1971.

I certify that I have caused a copy of the foregoing Motion to be served by hand upon the U.S. Attorney, United States Court House, Alexandria, Virginia, this 12th day of April, 1971.

JOEL E. HOFFMAN.

31 F.R. 13014 (October 6, 1966)

Food and Drug Administration

ANTIBIOTIC DRUGS

REPORTS OF INFORMATION FOR DRUG EFFECTIVENESS

There was published in the Federal Register of July 9, 1966 (31 F.R. 9426) information pertaining to the agreement by the National Academy of Sciences-National Research Council to assist the Food and Drug Administration in its review of the claims of effectiveness for drugs cleared through the new-drug procedures, pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act, from 1938 until October 10, 1962. This agreement also provides for a review of effectiveness of antibiotic drugs certified or exempted from certification under the provisions of section 507 of the act prior to October 10, 1962, as well as to antibiotic drugs cleared through the new-drug procedures but not subject to the certification provisions of section 507 of the act prior to October 10, 1962.

To facilitate this review and to facilitate a determination as to whether any certification or release should be rescinded or whether any regulation issued under section 507 of the act should be amended or repealed, and to give persons described below an opportunity to present for consideration of the reviewing experts the best data available to support the medical claims, this order is entered pursuant to section 507 of the act:

1. Each person engaged in manufacturing, compounding, processing, packing, or labeling any antibiotic drug in dosage form (other than distributor whose labeling is identical, except for such information as distributors' trade names, and addresses, to that under which such antibiotic drug is marketed by its supplier), which antibiotic drug is certified, released, or exempted from certification under the provisions of section 507 of the act on any basis other than approval of a form "5" after October 9, 1962, or an investigational exemption shall report the following in duplicate preferably on forms which have been revised by the National Academy of Sciences—National Research Council and which are available for this purpose from the Food and Drug Administration or any of its offices:

a. Date originally approved (whether approval is for a form 5, 6, or a new-drug application), new-drug application number,

if any, section of antibiotic regulations (21 CFR) providing specifications therefor, and whether prescription or over-the-counter drug.

b. Brand name of drug or preparation.

c. Applicant's (firm's) name and address.

d. Quantitative formula using established (nonproprietary) name of active ingredients.

e. Dosage form and route of administration. Where a new-drug application, form 5, or form 6 covers different routes of administration, separate forms should be used.

f. Current labels and package inserts (attach 10 copies of each to original of form; one copy of each to duplicate).

g. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, package insert, or brochure. Approximately 5 to 10 key references, if available (attach 10 copies of the list to original of form and one copy to duplicate).

h. Unpublished articles or other data pertinent to an evaluation of the claims (one copy only; attach to duplicate).

2. This report shall be made as promptly as possible and no later than 20 days from the date of this publication in the FEDERAL REGISTER, shall be plainly marked on the outside of the envelope or package "Special Antibiotic Report," and shall be addressed to the Director, Bureau of Medicine (or Director, Bureau of Veterinary Medicine, in the case of veterinary drugs), Food and Drug Administration, Washington, D.C. 20204.

3. The submission of this special report may be made without prejudice to any person's contention that he is not required by law to make the report.

4. This order is issued pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 507(g), 59 Stat. 463, as amended 76 Stat. 787, 21 U.S.C. 357(g)).

Dated: OCTOBER 3, 1966.

WINTON B. RANKIN,
Deputy Commissioner of Food and Drugs.

[F.R. Doc. 66-10899; Filed, Oct. 5, 1966; 8:48 a.m.]

33 F.R. 818 (January 23, 1968)

Food and Drug Administration

Drugs for Human Use Containing Rutin, Quercetin, Hesperidin, or Bioflavonoids

NEW-DRUG APPLICATIONS

The Food and Drug Administration published in the Federal Register July 9, 1966 (31 F.R. 9426), an announcement of the agreement by the National Academy of Sciences—National Research Council to assist the Food and Drug Administration in its review of the claims of effectiveness for the new drugs cleared between 1938 and October 10, 1962, on the basis of safety. Each holder of a new-drug application approved during that period was given an opportunity to present for the consideration of the reviewing experts the best data available to support the medical claims.

The Academy has submitted a report on a number of drugs containing rutin, quercetin, and citrus bioflavonoid compound. The Food and Drug Administration has considered the report and has concluded on the basis of the report and its own evaluations that there is no evidence that rutin, quercetin, hesperidin, or bioflavonoids are effective for use in man for any condition.

Under the Kefauver-Harris Amendments of 1962 to the Federal Food, Drug, and Cosmetic Act, lack of substantial evidence of effectiveness that a drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling is a basis for withdrawing approval of a new-drug application.

The Commissioner of Food and Drugs intends to publish a notice of opportunity for a hearing on a proposal to withdraw approval of all new-drug applications for drugs containing rutin, quercetin, hesperidin, or bioflavonoids alone and in combination with other drugs.

Promulgation of an order withdrawing approval of such new-drug applications will classify drugs containing any of these components as new drugs for which an approved new-drug application is not in effect. Any such drugs then on the market would be subject to regulatory proceedings. These components should also be withdrawn from dietary food supplements to avoid misbrandings.

Prior to initiating such action, however, the Commissioner of Food and Drugs invites all holders of new-drug applications which became effective under the new-drug provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505; 21 U.S.C. 355) for drugs containing rutin, quercetin, hesperidin, or bioflavonoids, and any persons who may be adversely affected by such action, to attend a meeting on January 31, 1968, at 1:30 p.m. in Room 804, Crystal Plaza No. 6, 2221 Jefferson Davis Highway, Arlington, Va. The purpose of the meeting will be to discuss the procedural matters involved in the proposed action of the Commissioner and to attempt to identity and resolve problems that may be anticipated as a result of the actions to be taken. Representatives who intend to participate in this meeting are asked to notify the agency in advance by writing to the Director, Bureau of Medicine, Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204, or calling his office (area code 703, 557–2686).

This announcement is made to give notice to interested persons of the proposed action and implementation of the NAS–NRC reports for the drugs listed above.

This statement is issued pursuant to the authority vested in the Secretary of Health, Education, and Welfare by the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 701(a), 52 Stat. 1050, as amended, 1052, as amended, 1055; 21 U.S.C. 352, 355, 371(a)) and delegated by him to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: JANUARY 15, 1968.

WINTON B. RANKIN,
Deputy Commissioner of Food and Drugs.

[F.R. Doc. 68–811 ; Filed, Jan. 22, 1968 ; 8 :45 a.m.]

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21 C.F.R. 130.39

§ 130.39 New-drug status opinions; statement of policy.

(a) Over the years since 1938 the Food and Drug Administration has given informal advice to inquires as to the new-drug status of preparations. These drugs have sometimes been identified only by general statements of composition. Generally such informal opinions were incorporated in letters that did not explicitly relate all of the necessary conditions and qualifications

such as the quantitative formula for the drug and the conditions under which it was prescribed, recommended, or suggested. This has contributed to misunderstanding and misinterpretation of such opinions.

(b) These informal opinions that an article is "not a new drug" or "no longer a new drug" require reexamination under the Kefauver-Harris Act (Public Law 87-781; 76 Stat. 788-89). In particular, when approval of a new-drug application is withdrawn under provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act, a drug generally recognized as safe may become a "new drug" within the meaning of section 201(p) of said Act as amended by the Kefauver-Harris Act on October, 1962. This is of special importance by reason of proposed actions to withdraw approval of new-drug applications for lack of substantial evidence of effectiveness as a result of reports of the National Academy of Sciences—National Research Council on its review of drug effectiveness; for example, see the notice published in the FEDERAL REGISTER of January 23, 1968 (33 F.R. 818), regarding rutin, quercetin, et al.

(c) Any marketed drug is a "new drug" if any labeling change made after October 9, 1962, recommends or suggests new conditions of use under which the drug is not generally recognized as safe and effective by qualified experts. Undisclosed or unreported side effects as well as the emergence of new knowledge presenting questions with respect to the safety or effectiveness of a drug may result in its becoming a "new drug" even though it was previously considered "not a new drug." Any previously given informal advice that an article is "not a new drug" does not apply to such an article if it has been changed in formulation, manufacture, control, or labeling in a way that may significantly affect the safety of the drug.

(d) For these reasons, all opinions previously given by the Food and Drug Administration to the effect that an article is "not a new drug" or is "no longer a new drug" are hereby revoked. This does not mean that all articles that were the subjects of such prior opinions will be regarded as new drugs. The prior opinions will be replaced by opinions of the Food and Drug Administration that are qualified and current on when an article is "not a new drug," as set forth in Subpart D (proposed) of this Part 130.

[33 F.R. 7758, May 28, 1968]

33 F.R. 9908 (July 10, 1968)

Food and Drug Administration

[Docket No. FDC-D-112; NDA No. 5960 etc.]

Drugs for Human use Containing Rutin, Quercetin, Hesperidin, or Any Bioflavonoids

Notice of Opportunity for Hearing on Proposal to Withdraw Approval of New-Drug Applications

In an announcement published in the Federal Register of January 23, 1968 (33 F.R. 818), holders of new-drug applications for drugs containing rutin, quercetin, hesperidin, or bioflavonoids, and other interested persons, were invited to attend a meeting to discuss a proposal to initiate proceedings to withdraw approval of such applications. The meeting was held on January 31, 1968, at which time the Food and Drug Administration invited the submission of additional scientific, medical information that might be pertinent to the question of the effectiveness of these drugs. The additional information received, considered together with other information available, did not provide substantial evidence of effectiveness of such drugs for use in man for any condition.

Therefore, notice is hereby given to:

Abbott Laboratories.
Arlington-Funk Labs. (Div. of U.S. Vitamin Corp.).
Best Pharmaceuticals.
The Blue Line Chemical Co.
Brayten Pharmaceutical Co.
The Central Pharmacal Co.
Direct Labs., Inc.
Grove Labs. (Subsidiary of Bristol-Myers).
K-V Pharmacal Co.
Lakeside Laboratories (Div. of Colgate-Palmolive Co.).
Lemmon Pharmacal.
Lloyd, Dabney & Westerfield, Inc.
The Maltine Co.
The S. E. Massengill Co.
Merck Sharp & Dohme (Div. of Merck & Co., Inc.).
Metro Med. Inc.
Nadin Co.

Nysco Labs., Inc.
Organon, Inc.
The E. L. Patch Co. (now Smith, Miller & Patch, Inc.),
The Paul Plessner Co.
Physicians Drug & Supply Co.
Rexall Drug & Chemical Co.
Rhodes Pharmacal Co., Inc.
Richlyn Laboratories.
Robin Pharmacal Co.
E. R. Squibb & Son (Div. Olin Mathieson Chemical Corp.)
R. J. Strasenburgh Co. (Div. of Wallace & Tiernan, Inc.)
Table Rock Labs., Inc.
U.S. Vitamin Corp.
Walker Labs., Inc. (Div. of Richardson-Merrell).
Henry K. Wampole & Co.

and to any interested person who may be adversely affected, that the Commissioner of Food and Drugs proposes to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of the following new-drug applications and all amendments and supplements thereto with respect to any drugs included in such applications which contain rutin, quercetin, hesperidin, or any bioflavonoid:

New Drug Applications Deemed Approved for Drugs Containing Rutin, Quercetin, Hesperidin, or Bioflavonoids

NDA No.	Drug name	Applicant's name and address
5060	Rutin Tablets	Abbott Laboratories, 14th and Sheridan Rd., North Chicago, Ill. 60064.
6020	Rutin Tablets; Rutorbin Tablets	E. R. Squibb & Sons, Division Olin Mathieson, Chemical Corp., 745 Fifth Ave., New York N.Y. 10022.
6070	Rutin Tablets	The Maltine Co., 745 Fifth Ave., New York, N.Y. 10022.
6158	Theoglycinate with Rutin and Phenobarbital.	Brayten Pharmaceutical Co., 1715 West 38th Street, Chattanooga, Tenn. 37400.
6291	Glytheonate with Rutin and Phenobarbital.	The E. L. Patch Co., now Smith, Miller & Patch, Inc., 902 Broadway, New York, N.Y. 10010.
6333	Synophyate Tablets	The Central Pharmacal Co., 116-128 East Third St., Seymour, Ind. 47274.
8360	Vir-I-Phyl	Lemmon Pharmacal, Temple Ave., Sellersville, Pa. 18900.

New Drug Applications Deemed Approved for Drugs Containing Rutin, Quercetin, Hesperidin, or Biovlavinoids—Continued

NDA No.	Drug name	Applicant's name and address
8036	Quertine (Queroctin, Abbott)	Abbott Laboratories, 14th Street and Sheridan Rd., North Chicago, Ill. 60600.
9074	Maxitate with Rauwolfia Compound Tablets.	R. J. Strasenburgh Co., Division of Wallace & Tiernan, Inc., 755 Jefferson Rd., Rochester, N.Y. 14603.
9118	Raufia Endote Tablets; Neo-Vir-I-Tin Encote Tablets.	Lemmon Pharmacal, Temple Ave., Sellersville, Pa. 18900.
9123	Loten Tablets	Lemmon Pharmacal, Temple Ave., Sellersville, Pa. 18960.
9255	Wolfinex	Lloyd, Dalbney & Westerfield, Inc., 3941 Brotherton Rd., Cincinnati, Ohio 45209.
9455	Ruserp-C	Lemmon Pharmacal, Temple Ave., Sellersville, Pa., 18900.
9588	Raulbexido Tablets	K-V Parmacal Co., 2503 South Hanley Rd., St. Louis, Mo. 63144.
9657	Rubexaial with Reserpine	Lemmon Pharmacal, Temple Ave., Sellersville, Pa. 18900.
9005	Neo-Semhyten Capsules	The S. E. Massengill Co., 513-529 Fifth St., Bristol, Tenn. 37620.
9640	Ranwolfia Serpeutina-Mannital Haxanitrate-Rutin Tablets.	Best Pharmaceuticals, 3725 Castor Ave., Philadelphia, Pa. 10124.
9681	Neo-Rauja Tablets	Table Rock Labs., Inc., 812 Hampton Ave., Grsonville, S.C. 29601.
9685	Raufwolfia Serpentiua-Mannitol Hexanitrate-Rutin-Veratrum Viride Tablets.	Robin Pharmacal Co., 57 Hope St., Brooklyn, N.Y. 11211.
9601	Restolic Tablets; Restolic Forte Tablets	Merck Sharp & Dohme, Division Merck & Co., Inc., West Point, Pa. 19476.
9914	Raumanultr-50 Tablets	Nysco Labs., Inc., 34-24 Vernon Blvd., Long Island City, N.Y. 11101.
9945	C.V.P.; C.V.P. w/Vitamin K; Bivan Tablets; Duo-C.V.P. w/Vitamin K Capsules.	U.S. Vitamin Corp., 26 Vark St., Yonkers, N.Y. 10701
10000	Tenserina Tablets (Spanish name); Tenserina Tablets (English name).	Abbott Laboratories, 14th and Sheridan Rd., North Chicago, Ill. 60064.
10013	"Bio-Flav" Citrus Bioflavonoid Complex and Vitamin C Tablets.	Nadin Co., 1813 Flower St., Glendale, Calif. 91201.
10046	Capilon Tablets	The Paul Plessner Co.,635 30th Ave. North, Post Office Box 7087, St. Petersburg, Fla. 33734.
10063	Citroid Capsules	Grove Labs., Subsidiary of Bristol-Myers, 8420 Delmar Blvd., Post Office Box 7300, St. Louis, Mo. 63177.
10114	Mannitrau Tablets	Richlyn Laboratories, 3725 Castor Ave., Philadelphia, Pa. 19124.
10130	Rauman Tablets	Direct Labs., Inc., 337 Genesee St., Post Office Box 708, Buffalo, N.Y. 14240.
10136	Routenal Tablets	Physicians Drug & Supply Co., 1458 Chestnut Ave., Hillside, N.J. 07205.
10212	Flavoserp	The Blue Line Chemical Co., 302 South Broadway, St. Louis, Mo. 63102.
10310	Prevoids	Rhodes Pharmacal Co., Inc., 41 East Oak St., Chicago, Ill. 60611.
10772	Bioresp-C	Henry K. Wampole & Co., 35 Commerce Rd., Stamford, Conn. 06902.
10816	Adrestat	Organon, Inc., 375 Mount Pleasant Ave., West Orange, N.J. 07052.
11050	Bioscreen	The Central Pharmacal Co., 116-128 East Third St., Seymour, Ind. 47274.

New Drug Applications Deemed Approved for Drugs Containing Rutin, Quercetin, Hesperidin, or Bioflavonoids—Continued

NDA No.	Drug name	Applicant's name and address
11051	Citroid Compound	Grove Labs., Subsidiary of Bristol-Myers, 800 Delmar Blvd., Post Office Box 720, St. Louis, Mo. 63177.
11052	Citroid Compound	Do.
11186	Citroid Jr.	Do.
11214	Super Anagac Cough Syrup	Rexall Drug & Chemical Co., 8480 Beverly Blvd., Los Angeles, Calif. 90054.
11240	Serbio Capsules	Metro Med. Inc., 2510 South Blvd., Houston, Tex. 77006.
11474	Prednyl Tablets	Arlington-Funk Labs., Division of U.S. Vitamin Corp., 26 Vark St., Yonkers, N.Y. 10701.
11475	Prednis-C.V.P. Capsules	Do.
11057	Dacill-O R	Lakeside Laboratories, Division of Colgate-Palmolive Co., 1707 East North Ave., Milwaukee, Wis. 53201.
12261	Natorexic Tablets	Walker Labs., Inc., Division of Richardson-Merrell, 1 Bradford Rd., Mount Vernon, N.Y. 10551.

It is proposed to withdraw approval on the grounds that there is a lack of substantial evidence that rutin, quercetin, hesperidin, or any bioflavonoid has the effect which the drugs purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof, or that such articles alone, or as added components with other drugs, are effective for use in man for any condition.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give each applicant and any interested person who would be adversely affected by an order withdrawing such approval an opportunity for a hearing at which time such persons may produce evidence and arguments to show why approval of any new-drug application listed herein should not be withdrawn. Promulgation of the proposed order will cause any drug for human use containing any rutin, quercetin, hesperidin, or bioflavonoid to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

Within 30 days from the date of publication of this notice in the FEDERAL REGISTER, such persons are required to file with the Hearing Clerk, Department of Health, Education, and Welfare, Office of the General Counsel, Food and Drug Division,

Room 5440, 330 Independence Avenue SW., Washington, D.C. 20201, a written appearance electing whether:

1. To avail themselves of the opportunity for a hearing; or
2. Not to avail themselves of the opportunity for a hearing.

If such persons elect not to avail themselves of the opportunity for a hearing, the Commissioner without further notice will enter a final order withdrawing the approval of the new-drug application. Failure of such persons to file such a written appearance of election within 30 days following the date of publication of this notice in the FEDERAL REGISTER will be construed as an election by such persons not to avail themselves of the opportunity for a hearing.

The hearing contemplated by this notice will be open to the public except that any portion of the hearing that concerns a method or process that the Commissioner finds is entitled to protection as a trade secret will not be open to the public, unless the respondent specifies otherwise in his appearance.

If such persons elect to avail themselves of the opportunity for a hearing by filing a timely written appearance of election, a hearing examiner will be named by the Commissioner and he shall issue a written notice of the time and place for the hearing.

This notice is issued under the authority contained in the Federal Food, Drug, and Cosmetic Act. (sec. 505, 52 Stat. 1052, as amended; 21 U.S.C. 355) and delegated to the Commissioner (21 CFR 2.120).

Dated: JUNE 28, 1968.

JAMES L. GODDARD,
Commissioner of Food and Drugs.

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35 F.R. 16332 (October 17, 1970)

Food and Drug Administration

[Docket No. FDC-D-112; NDA No. 9-965 etc.]

DRUGS CONTAINING RUTIN, QUERCETIN, HESPERIDIN, OR ANY BIOFLAVONOIDS

NOTICE OF WITHDRAWAL OF APPROVAL OF NEW-DRUG APPLICATIONS

On July 10, 1968, there was published in the FEDERAL REGISTER (33 F.R. 9908) a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e) withdrawing ap-

proval of new-drug applications listed therein on the ground that there is a lack of substantial evidence that rutin, quercetin, hesperidin, or any bioflavonoid has the effect which the drugs purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof, or that such articles alone, or as added components with other drugs, are effective for use in man for any condition.

The firms listed below elected to avail themselves of the opportunity for a hearing. By letters of July 7, 1970, these firms were notified that their request for a hearing should be amended to comply with the regulations published in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250) describing the scientific content of adequate and well-controlled clinical investigations and setting forth the procedural requirements for requesting public hearings and demonstrating that there is a genuine and substantial issue of fact that requires a hearing. Such amendment to the request for hearing has not been received. Counsel for U.S. Vitamin Pharmaceutical Corp. responded to the July 7, 1970 letter and requested a stay of any further proceedings in the proposal to withdraw approval of their new drug applications, citing pending litigation in the U.S. District Court for the Eastern District of Virginia and the U.S. District Court for the District of Delaware as grounds for delay. The fact that there is pending litigation does not provide sufficient grounds for the request, and the Commissioner concludes that further delay of the proposed withdrawal of approval is not justified.

NDA No.	Drug name	Applicant's name and address
9-965	C.V.P.; C.V.P. w/Vitamin K; Bivan Tablets; Duo-C.V.P. w/Vitamin K Capsules.	U.S. Vitamin Corp., 26 Vark St., Yonkers, N.Y. 10701.
11-474	Prednyl Tablets	Arlington-Funk Labs., Division of U.S. Vitamin Corp., 26 Vark St., Yonkers, N.Y. 10701.
11-475	Prednis-C.V.P. Capsules	Do.

The Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505 (e)), 52 Stat. 1053, as amended; (21 U.S.C. 355(e)), and under the authority delegated to him (21 CFR 2.120), finds that on the basis of new information before him with respect to each of said drugs, evaluated together with the evidence available to him when each application was approved, there is a lack of substantial evidence that each of the drugs will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Therefore, pursuant to the foregoing findings, approval of the above new-drug applications, and all amendments and supplements thereto, is withdrawn effective on the date of the signature of this document.

Dated: OCTOBER 15, 1970.

SAM D. FINE,
Associate Commissioner for Compliance.

[F.R. Doc. 70-14072; Filed, Oct. 16, 1970; 8:50 a.m.]

FEBRUARY 28, 1961.

Dr. Ralph G. Smith,
Department of Health, Education & Welfare,
Food & Drug Administration,
New Drug Branch,
Washington 25, D.C.

DEAR DR. SMITH: Attached herewith you will find a list of various effective New Drug Applications.

We should appreciate very much your advice with respect to the current status of these applications—that is, whether or not they are still considered to be "new drugs".

Thank you for your kind cooperation in this matter.

Very truly yours

EPHRAIN GUNSBERG,
Assistant to the Vice President,
U.S. Vitamin & Phamaceutical Corporation.

	NDA
Vi-Syneral Inj	6373
Vitamin A Inj. Vst., no longer marketed	6521
E-Toplex Inj., no longer marketed	6822
Aquasol A Parenteral	6823
Co-Salt	7150
Dodecavite	7152
Enelone, no longer marketed	7272
Enescorb, no longer marketed	7851
Methischol Inj	8326
Tisin, no longer marketed	8503
H.V.I.	8809
Stanone, no longer marketed	9002
Dilatol (Arlidin) Tablets	9367
Pantho-F	9794
Dilatol (Arlidin) Inj	9813
C.V.P.	9965
Dodecatrate, never marketed	11-004
Prednyl	11-474
Prednis-CVP	11-475
DBI	11-624
Trypp	12-149
Emivan Tablets	12-451
Emivan Inj	12-452

NDA 9367 12452
9013 11475
11624 11474
12149 9794
12451 8099

U.S. Vitamin & Pharmaceutical Corporation
Attention: Mr. Ephrain Gunsberg
250 East 43rd Street
New York 17, New York

GENTLEMEN: This will acknowledge your letter of February 23, 1961, submitted personally by Mr. Ephrain Gunsberg on March 1, 1961, requesting our opinion on the new drug status of the products for which you hold effective new drug applications.

We are not furnishing a complete answer at this time. With respect to those products on which we are not replying, it is suggested that you submit a separate letter of inquiry on each one furnishing some information on marketing experience and enclosing five copies of your current labels and labeling, or if not marketed those which were previously used. On checking a number of the older applications, it is noted that final printed labeling was not submitted as requested in our "effective letters." Further, we are not sure that some products have been marketed—for example, E-Toplex Injection NDA 6322, Tisin NDA 8503 and Stanche NDA 9002.

The following products are still regarded as new drugs:

Arlidin Tablets	NDA 9367
Arlidin Injection	9013
DBI	11624
Trypp	12149
Emivan Tablets	12451
Emivan Injection	12452

In our opinion the following products are not new drugs when distributed under the labeling provided for in the respective effective new drug applications:

Prednis-CVR	NDA 11475
Prednyl	11474
Pantho-F	9794
M.V.I.	8800

Copies of the final printed labels and labeling are requested for Pantho-F.

We will be pleased to comment on the other products if furnished with additional material as requested above.

Sincerely yours,

RALPH G. SMITH, M.D.,
Director, New Drug Branch,
Bureau of Medicine.

MAY 16, 1961.

Dr. RALPH G. SMITH
U.S. Department of Health, Education, and Welfare
Food and Drug Administration
New Drug Branch
Washington 25, D.C.

Re: N.D.A. No. 9965 C.V.P. Products

DEAR DR. SMITH: This is in reference to your letter of April 19, 1961 in response to our letter of February 28, 1961 concerning the new drug status of C.V.P. products.

In accordance with your request, we are submitting herewith five (5) copies of the labels and labeling currently being used for these products, which we have been marketing continuously for at least ten years.

It is our recollection that the C.V.P. class of products were no longer considered to be new drugs a short time after the N.D.A. became effective.

We should appreciate very much your confirmation of the above.

Thank you for your kind cooperation in this matter.

Very truly yours,

LOUIS FREEDMAN, Ph.D.,
Vice President in Charge of Research,
U.S. Vitamin & Pharmaceutical Corporation.

U.S. VITAMIN & PHARMACEUTICAL CORPORATION,
800 Second Avenue, New York 17, N.Y., October 5, 1965.

Department of Health, Education, and Welfare
Food and Drug Administration
Washington, D.C. 20204

Attention: George P. Larrick, Commissioner of Food and Drugs.

DEAR MR. LARRICK: This is in reference to your letter of May 27, 1965, requesting information under the reporting re-

quirements of Section 130.35 of the Regulations for the following products:

1. Pantho-F Cream, 0.2%
2. Pantho-F Cream, 1%
3. C.V.P. with vitamin K Tablets
4. C.V.P. with vitamin K Syrup
5. Prednis—C.V.P. Capsules

In view of the subsequent correspondence between Joseph Stetler, Esq., of the Pharmaceutical Manufacturers Association, and yourself, and our desire to submit promptly any information which we believe will be useful in your evaluation of the above-identified products, we have carefully reviewed our files. In our opinion, there is nothing in them which reveals that the products are not safe and effective for the purposes for which they are marketed.

This information is being submitted without prejudice to our position that you do not have the legal authority to require reports with respect to drugs which are no longer "new drugs", and the submission of the above information does not constitute any implied admission as to the legal status of the products concerned.

Very truly yours,

EPHRAIM GUNSBERG,
Vice President, Technical Operations,
U.S. Vitamin & Pharmaceutical Corporation.

LAW OFFICES, WALD, HARKRADER, NICHOLSON & ROSS,
1320 Nineteenth Street, N.W., Washington, D.C. 20036,
August 7, 1970.

Re: Dkt. No. FDC–D–112.

CHARLES C. EDWARDS, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
Department of Health,
Education and Welfare
Parklawn Building
Rockville, Maryland 20850

DEAR DOCTOR EDWARDS: USV Pharmaceutical Corporation, holder of three new drug applications involved in the captioned proceeding (Nos. 9665, 11–474 and 11–475), has re-

ceived your letters of July 7, 1970. We understand those letters to require compliance with the "Hearing and Scientific-Content Regulations", published last May 8, (35 Fed. Reg. 7250), as a predicate to a hearing on the Commissioner's proposal of July 10, 1968 to withdraw approval of those NDA's. The company requests a stay of all further proceedings herein as to these NDA's for the following reasons:

1. There is no need for *any* proceedings as to these NDA's if the products alleged by FDA to be "covered" thereby are not new drugs. That issue is now pending for judicial determination on cross-motions for summary judgment in *USV Pharmaceutical Corp.* v. *Richardson, et al.*, Civil No. 4915–A in the United States District Court for the Eastern District of Virginia. The motions have been fully briefed. In the course of a pretrial conference on July 17, 1970, the Court ruled that whether the suit can be disposed of on the motions will shortly be decided, and that any trial which may be found necessary will in any event be held on October 23, 1970. The new-drug status of the products alleged by FDA to be "covered" by the company's three NDA's will thus be judicially determined within the next few months.

2. The validity of the May 8 "Hearing and Scientific-Content Regulations" is already before the United States District Court for the District of Delaware in *Pharmaceutical Mfrs. Ass'n* v. *Richardson, et al.*, Civil No. 3946. We believe that for the reasons alleged by PMA the May 8 regulations are invalid, and that in any event it would be inappropriate to apply them to the pending proceeding, in which all prerequisites to a hearing then in force were fully met as long as two years ago. This latter issue need not be reached, however, if the May 8 regulations are invalid as alleged in the pending litigation.

Orderly accommodation of judicial and administrative authority thus requires that all proceedings as to the NDA's involved in this proceeding be stayed. The stay should continue at least until the issues before the Virginia and Delaware courts are resolved.

USV requests that if a stay is denied the company be given at least thirty days from receipt of notice of the denial to file a further response to your letters of July 7. The company further requests that all communications in this proceeding be addressed to this firm as its counsel of record in compliance with 5 U.S.C. § 500(f).

This letter is without prejudice to the company's position that in the event of administrative adjudication with respect to these NDA's you may be disqualified from participating in the decision by reason of having pre-judged the issues, as evidenced by statements and allegations advanced in the defense of *USV Pharmaceutical Corp.* v. *Richardson, supra.*

We should appreciate an opportunity to meet with you at your early convenience to discuss this proposal for a stay and the future course of these proceedings.

Respectfully submitted,

WALD, HARKRADER,
NICHOLSON & ROSS
ROBERT L. WALD,
Counsel for USV Pharmaceutical Corporation.

DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE,
FOOD AND DRUG ADMINISTRATION,
WASHINGTON, D.C. 20204,
October 14, 1970.

Mr. Robert L. Wald
1320 Nineteenth Street, N.W.
Washington, D.C. 20036

DEAR MR. WALD: This replies to your letter of August 7, 1970, in response to ours of July 7, 1970, in which you request a stay of all further proceeding involving your client's new drug applications 9965, for C.V.P., C.V. with Vitamin K, Bivam Tablets, and Cuo–C.V.P. with Vitamin K Capsule 11–474 for Prednyl Tablets; and, 11–475 for Prednis–C.V.P. Capsules.

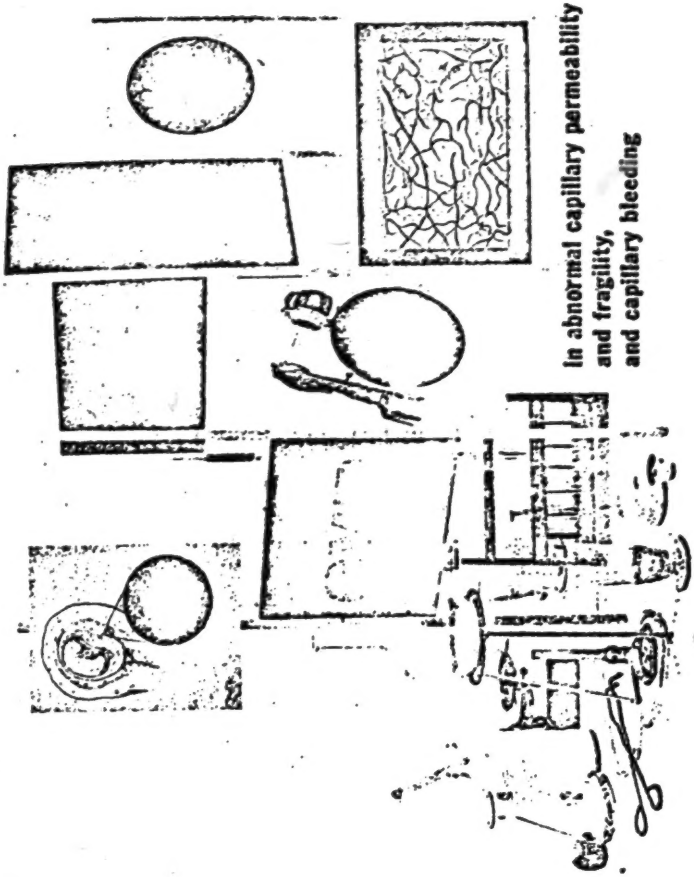
We regard these products as new drugs as defined in the Federal Food, Drug, and Cosmetic Act. Our letter of July 7, 1970, suggested the request for a hearing be amended within 30 days from receipt of that letter, by submitting a well-organized and full-factual analysis of clinical and other investigational data that USV Corporation is prepared to prove in a hearing, setting forth specific facts showing that it is a genuine and substantial issue of fact that requires a hearing. To date, no amendment has been received.

Accordingly, we conclude that no useful purpose will be served by delaying the processing of a final order to withdraw approval of the subject new drug applications. The pending litigation in the United States District Court for the Eastern District of Virginia and the United States District Court for the District of Delaware do not provide sufficient grounds to further delay these proceedings.

Your request for a 30-day extension, in the event of our denial of a stay, is also denied.

Sincerely yours,

CHARLES C. EDWARDS, M.D.,
Commissioner of Food and Drugs.



Exclusive Water-Soluble Citrus Bioflavonoid Compound With Ascorbic Acid*

"The Integrity of the Capillaary System Is an Essential Factor in Health and Disease." [16]

The state of the capillary walls with respect to permeability is "of the utmost importance in maintaining the nutrition of the tissues and in maintaining the normal distribution of fluids within and without the vascular system." [17] Complex vital processes are dependent on the functional health of these minute blood vessels.

The capillary wall is a single layer of endothelial cells bound together by an intercellular cement, with millions of pores which serve as selective sieves for plasma. The normal capillary wall is impermeable to serum albumin and serum globulin. In certain pathologic conditions, these pores enlarge, permitting the passage of larger protein molecules (increased capillary permeability) and, in certain later stages, the cement may be so weakened as to cause a rupture of the vessel (capillary fragility).[16]

In diabetes, hypertension, threatened and habitual abortion, purpuras, epistaxis, viral and bacterial infections, periodontal diseases, peptic ulcer and other conditions, abnormal permeability and fragility of capillaries frequently occur.[5 8 13 15 16] Many drugs (e.g., antibiotics, sulfonamides, isoniazid, certain steroids, analgesics and antiarthritics), numerous commonly used chemicals, as well as viruses and bacterial toxins increase capillary permeability and fragility.[16 29]

Capillary Fragility Widespread

In apparently healthy subjects a progressive increase in capillary fragility is common after age 20 and extreme fragility occurs in 80 per cent of individuals past 60.[7] All hypertensive diabetics of a large series showed increased capillary fragility.[15] Abnormal capillary fragility was found in 80 per cent of patients with rheumatic fever,[19] in 90 per cent with spontaneous purpura, in 49 per cent of allergic patients,[20] in 60 to 80 per cent of habitual aborters.[10 11] Injury to the capillary system has been reported in various infections; e.g., viral hepatitis, poli-

*Made by an exclusive patented process.

myelitis, smallpox, measles, mumps, rabies, influenza, common cold, encephalomyelitis and primary atypical pneumonia.[14]

Permeability

How C.V.P. Helps Overcome Abnormal Capillary Permeability

C.V.P. is a water-soluble biologically active flavonoid compound from citrus peel and pulp combined with ascorbic acid. C.V.P. acts to maintain the integrity of capillary walls by strengthening the intercellular ground substance or cement which binds together the endothelial cells.[16] This helps to increase capillary integrity and aids in preventing and overcoming abnormal capillary permeability, fragility, and bleeding. The water-soluble bioflavonoid compound of C.V.P. is, by itself, highly active in a number of biological and chemical tests. Clinically, in the correction of capillary fault, certain bleeding states do not respond to vitamin alone, but do respond to the combination of bioflavonoids and ascorbic acid.[16]

Physiologic Effects of C.V.P.

The physiologic properties of the bioflavonoids (biologically active flavonoids) have been extensively investigated. While the various mechanisms are not yet completely understood, these physiologic actions have been demonstrated:

1. Anti-hemorrhagic effect.—In experimental studies, the water-soluble bioflavonoid complex available exclusively in C.V.P. protected against the capillary fragility and hemorrhage-producing effects of bacterral polysaccharide in tumor-bearing rats.[2 45] Clinically, the anti-hemorrhagic effect of C.V.P. has been demonstrated in such bleeding conditions as habitual abortion,[31] retinitis,[8] bleeding duodenal ulcer and ulcerative colitis,[21 39] epistaxis,[44] purpuras,[3 39] tonsillectomy bleeding and other otolaryngologic procedures,[21 44] periodontal disease,[25 26] hemorrhagic diatheases.[3]

2. Anti-inflammatory effect.—C.V.P.'s water soluble complex is actively anti-inflammatory. It definitely inhibits the proteolytic action giving rise to such substances as histamine and leukotaxine which produce the abnormal capillary premeability associated with inflammation.[2 4 30]

3. Inhibition of hyalaronidase.—The "spreading factor," which might cause increased capillary permeability, acts to

dissolve the intercellular cement substance. Bioflavonoids in combination with ascorbic acid markedly inhibit the activity of this enzyme.[36]

4. Inhibition of histamine.—Several investigators have postulated that bioflavonoids have an antianaphylactoid action. Among them is Ungar [37] who showed that bioflavonoids inhibit release of histamine from blood cells.

5. Decreases excessive bleeding time when this is due to increased capillary permeability.[37]

6. Virus inhibitory.—In vivo and in vitro experiments indicate that the water-soluble bioflavonoid complex of C.V.P. may have anti-viral activity.[34 40]

7. Relationship between bioflavonoids and ascorbic acid.—Bioflavonoids increase the retention of ascorbic acid in the blood and adrenal glands of experimental animals.[34] Patients with certain types of capillary hemorrhage respond better to a combination of the bioflavonoids and ascorbic acid than to ascorbic acid alone.[16] The water-soluble citrus bioflavonoids (C.V.P.) have been reported to prevent scurvy in patients placed experimentally on a low ascorbic acid diet.[41]

C.V.P. Is An Exclusive Compound—Superior to Hesperidin, Rutin

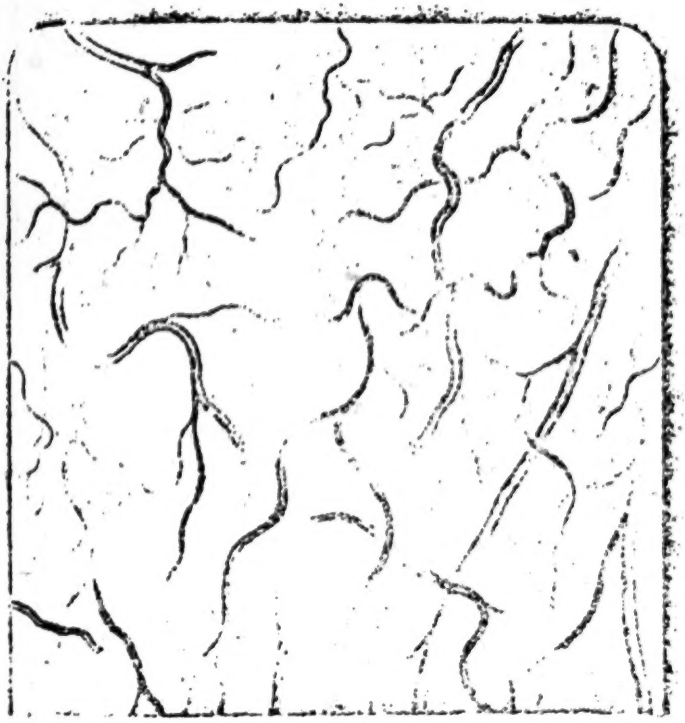
C.V.P. is different from other flavonoid products. Only C.V.P. provides the many active water-soluble bioflavonoid factors of the whole citrus bioflavonoid complex. C.V.P. (due to special processing) is relatively low in hesperidin, naringin and other compartively insoluble and inactive flavonoids found in citrus.

"The very low solubility of hesperidin and rutin in water is sufficient to explain their relatively low activity by the oral route." [6] Hesperidin, naringin, and certain other water-insoluble flavonoids are inactive in biologic tests in which C.V.P. is highly active.[4 30 45] Present evidence in our laboratories supports the view that the apparent activity of certain preparations containing hesperidin given orally is due to traces of active flavonoids

which may accompany the insoluble hesperidin. As demonstrated in laboratory experiments, C.V.P. has a many times greater effect than rutin in maintaining capillary integrity.[3,45]

Clinically Tested, Safe, Well Tolerated

Laboratory and clinical investigations with C.V.P., starting in 1946, have demonstrated its high degree of safety and its value in restoring and maintaining capillary integrity. C.V.P. is well tolerated and free from side effects, even when given continuously for long periods.





TO HELP CORRECT FAULTY CAPILLARY PERMEABILITY AND FRAGILITY AND RESTORE CAPILLARY INTEGRITY . . . AND THUS AID IN PREVENTING AND CHECKING CAPILLARY BLEEDING, AND NORMALIZING CAPILLARY FLUID INTERCHANGE IN . . .

HABITUAL AND THREATENED ABORTION; POSTPARTUM BLEEDING

Three out of every four habitual aborters treated with C.V.P. from early pregnancy successfully delivered normal, healthy infants.[31,46] Two out of every three threatened aborters were enabled, on C.V.P. treatment, to complete gestation and deliver live, healthy babies. "There was a decrease in postpartum bleeding in the series of treated patients as compared with nontreated patients." [31]

EPISTAXIS, OTOLARYNGOLOGY, TONSILLECTOMY

C.V.P., or C.V.P. with vitamin K, produced a "decided decrease in oozing" after the surfaces were cut in tonsillectomies and adenoidectomies; "a sharp decrease in the number of nose-

bleed recurrences" in epistaxis; rapid reduction of swelling and postoperative discoloration in rhinoplasties, otoplasties, septal resections and other otolaryngologic surgery; "encouraging results" in the treatment of acute serous otitis.[24] In patients with epistaxis, C.V.P. with vitamin K "almost invariably prevented recurrences." [44]



PURPURA, ECCHYMOSIS

In patients under treatment with corticosteroids, C.V.P. may be effective in protecting against or overcoming purpura, ecchymosis and other manifestations of capillary fault commonly resulting from prolonged steroid therapy.[33] C.V.P. helps prevent and arrest capillary hemorrhage associated with non-thrombocytopenic purpura.[8]

HYPERTENSION

Abnormal capillary permeability and fragility occur in many hypertensives and may lead to retinal hemorrhage and other

vascular accidents.[1] C.V.P. helps to increase capillary resistance and thus may act to prevent these complications.[6]

"LITTLE STROKES"

Accepting the biological premise that capillary injury and capillary hemorrhage play an important role in "little strokes," a group of investigators [35] treated with C.V.P. a small series of 13 patients who had had one to four previous "little strokes." In this preliminary report there was no further occurrence of "little strokes" in 10 cases during the one to three years of therapy.

DIABETIC RETINITIS, OCULAR DISORDERS

"C.V.P. provides the ophthalmologist with a valuable therapeutic aid in the management of certain ocular diseases . . . in which increased capillary fragility and permeability are the principal or complicating factors" (diabetic and hypertensive retinopathies, central angiospastic retinopathy, vitreous opacities, macular degeneration). It results in "more rapid clearing of hemorrhages, when present, and improvement in visual acuity." [33]

C.V.P. may help protect the retinopathy-prone diabetic or hypertensive from developing this all-too-frequent vascular complication.[5,9]



495-151—73——21

BLEEDING GUMS, GINGIVITIS, PYORRHEA, PERIODONTAL CONDITIONS

In chronic gingivitis, chronic pyorrhea and periodontosis—often in cases of long duration and unresponsive to other therapy—"the salutary effect (of C.V.P.) was evident and often dramatic." [26,27] C.V.P. "can be used very effectively" as preventive or inhibitory therapy in known or potential hemorrhagic cases.[26]

MENORRHAGIA

C.V.P. helps reduce bleeding in menorrhagia and metrorrhagia.[46]

RH INCOMPATIBILITY

A small number of Rh negative women, who had previously delivered erythroblastotic infants, were started on C.V.P. before the 14th week of pregnancy. No significant rise in antibody titer was observed. All babies were born alive, healthier and either not affected, or less affected, than those of previous births.[21,22]

CERTAIN RESPIRATORY CONDITIONS

Significant ameliorative effects were obtained with C.V.P. in colds, influenza and certain other respiratory infections.[13,15] "Our results strongly suggested that the bioflavonoids operate in the infections, at least in part, by restoring normal capillary integrity."

Investigators,[42,43] who employed C.V.P. therapeutically in industrial plants, reported symptomatic relief in the common cold and other respiratory infections and impressive reduction in absenteeism.

RHEUMATOID ARTHRITIS

Clinical studies [33,38,45] suggest that C.V.P. has a salutary effect on the capillary syndrome in the affected areas in rheumatoid arthritis and acute bursitis. C.V.P. is "a valuable adjunct in the management of rheumatoid arthritis" and is particularly helpful in preventing purpura and other evidence of capillary damage resulting from corticosteroids.[33]

HEMORRHAGIC DUODENAL ULCER AND ULCERATIVE COLITIS

Uncomplicated hemorrhagic duodenal ulcer and ulcerative colitis responded to treatment with C.V.P. in a most satisfactory manner. Bleeding was arrested within a few days.[21,39]

HEMORRHAGIC CYSTITIS

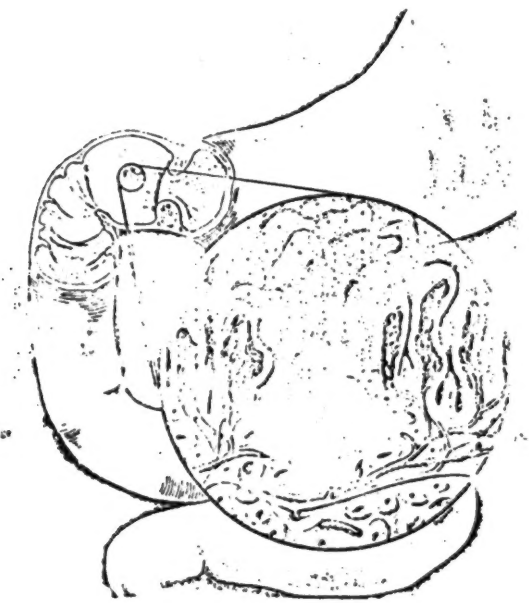
In a preliminary study, C.V.P. was found to check bleeding and inflammation in hemorrhagic cystitis by acting to reduce abnormal capillary permeability and fragility. Symptomatic relief was rapid and pathogenic organisms disappeared from the urine within five days.[23]

POSTOPERATIVE BLEEDING

Administered pre- and postoperatively, C.V.P. had a salutary effect on capillary bleeding and hastened healing following surgical procedures.[5,24]

RADIATION THERAPY

C.V.P. helps protect against capillary damage due to radiation and minimizes radiation erythemata. Does not reduce sensitivity of malignant tissue to x-ray irradiation.[12]



a dilated skin capillary hemorrhage

safe, simple, effective,
in the control of
abnormal capillary permeability,
fragility and
resultant bleeding

C.V.P.

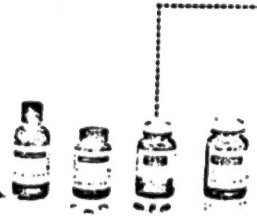
Each C.V.P. capsule, or 5 cc.
(approx. 1 teaspoonful) syrup, provides:
CITRUS BIOFLAVONOID COMPOUND* . . . . . 100 mg.
ASCORBIC ACID (Vitamin C) . . . . . 100 mg.

duo-C.V.P.

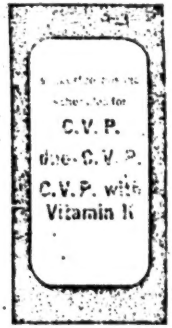
for use in patients in whom low prothrombin levels may accompany abnormal capillary permeability and fragility.

Each duo-C.V.P. with Vitamin K tablet, or 5 cc.
(approx. 1 teaspoonful) syrup, provides:
CITRUS BIOFLAVONOID COMPOUND* . . . . . 100 mg.
ASCORBIC ACID (Vitamin C) . . . . . 100 mg.
MENADIONE (vitamin K) . . . . . 0.05 mg.

*Original and exclusive bioflavonoid compound containing the many active water-soluble factors of the whole natural citrus bioflavonoid complex relatively free (due to special processing) of hesperidin, naringin and other comparatively insoluble and inactive flavonoids found in citrus.



supplied:
C.V.P. — Bottles of 100, 500 and 1000 capsules; 4 oz., 16 oz. and gallon syrup.
duo-C.V.P. — Bottles of 50, 100, 500, and 1000 capsules.
C.V.P. with Vitamin K — Bottles of 100 and 1000 tablets; 4 oz., 16 oz. and gallon syrup.





note: This exclusive water-soluble citrus bioflavonoid complex is also available in combination with multiple vitamins and minerals for prophylactic nutritional supplementation as BIVAM tablets.

	in divided doses daily . . .		
	C.V.P. (capsules or tsp. syrup)	duo-C.V.P. (capsules)	C.V.P. with Vitamin K (tablets or tsp. syrup)
adults For the prevention or treatment of abnormal capillary permeability and fragility, and capillary bleeding in . . .			
hypertension, diabetes, retinal hemorrhage, prevention of "little strokes"	3 to 6	2 to 3	3 to 6
purpurea, rheumatoid arthritis	3 to 12	2 to 6	—
habitual abortion, Rh incompatibility	3 to 6	2 to 3	3 to 6
bleeding in pregnancy; threatened abortion	9 to 15	5 to 8	9 to 15
urinary and enteric hemorrhage (cystitis, duodenal ulcer, colitis)	6 to 12	3 to 6	6 to 12
bleeding gums, epistaxis, gingivitis, pyorrhea, periodontal conditions	6 to 9	3 to 5	6 to 9
surgery, x-ray treatment (for one week prior to surgery or x-ray treatment, during x-ray therapy and convalescence)	6	3	6
"common cold", certain virus and respiratory conditions	9 to 12 for two days; 6 for next two or more days	4 to 6 for two days; 3 for next two or more days	—
maintenance dose to prevent recurrence of capillary damage	1 to 3	1 to 2	—
children therapeutic dose in treatment of increased capillary permeability and fragility, and capillary bleeding	3 to 6	2 to 3	3 to 6
tonsillectomy, other surgery (5 to 10 days before and for a like period following surgery)	3 to 6	2 to 3	3 to 6
maintenance dose	1 to 3	1 to 2	—

U.S. vitamin corporation

In the United States District Court, for the Eastern District of Virginia

[Caption omitted]

Deposition of Theodore H. Spaet, a witness, taken by plaintiff pursuant to subpoena duces tecum dated August 28, 1969, at 245 Park Avenue, New York, N.Y., 10017, on September 4, 1969 at 10:00 a.m. before Charles Richer, a Shorthand Reporter and Commissioner of Deeds of the City of New York

[2] APPEARANCES

Messrs. *Wald, Harkrader & Rockefeller*, Attorneys for plaintiff, 1225 Nineteenth Street, NW., Washington, D.C.

By: *Joel E. Hoffman, Esq., Miss Selma M. Levine, Robert L. Wald, Esq.*, Of Counsel.

Joanne S. Sisk, Esq., and *Lillian Scott, Esq.*, Attorneys for Food, Drugs & Environmental Health Division, Office of General Counsel, United States Department of Health Education and Welfare, Washington, D.C.

J. Joseph Belson, Esq., Assistant to the Director, Division of Case Guidance, Bureau of Compliance, U.S. Food and Drug Administration, 200 C Street, SW., Washington, D.C.

Also present: *Dr. Harvey S. Sadow.*

[Theodore H. Spaet, called as a witness by plaintiff, having been first duly sworn by a Commissioner of Deeds of the City of New York, testified as follows:]

Examination by MR. HOFFMAN:

Q. Dr. Spaet, I wonder if you could give us your full [3] name, again, for the record?

A. Middle initial or full?

Q. The middle initial will suffice.

A. Theodore H. Spaet.

Q. And your address?

A. 23 Rectory Lane, Scarsdale, New York.

Q. Are you here today pursuant to a subpoena?

A. I am.

Mr. HOFFMAN. Mr. Reporter, I would like you to mark the subpoena as Deposition Exhibit 1 for indentification.

(Subpoena dated August 28, 1969, addressed to Dr. Theodore H. Spaet, 23 Rectory Lane, Scarsdale, N.Y., marked Plain-

tiff's Exhibit 1 for identification as of this date.)

Mr. HOFFMAN. I suppose the record should show that there is attached to Exhibit 1 a single-page schedule listing documents.

Q. Dr. Spaet, I show you Exhibit 1. Can you tell me if this is the subpoena to which you just referred?

A. It is.

Q. Doctor, what is your occupation?

A. Physician.

Q. Are you a practicing physician or a teaching phy [4] sician or both?

A. A description of my situation, I think, would be a full-time employee of Montefiore Hospital in the Albert Einstein College of Medicine, and my job is to run the Department of Hematology at Montefiore Hospital and also to serve on the faculty of the College.

Q. Is your official title Chairman of the Department?

A. No, my title is Head.

Q. Dr. Spaet, have you been a member of a panel established by the Drug Efficacy Study of the National Academy of Sciences' National Research Council?

A. I presume this is the proper nomenclature. If it is, I was.

Q. It is. I am sure Mrs. Sisk will tell you if it is not.

Dr. Spaet, did you bring with you any documents pursuant to the subpoena, Exhibit 1?

A. I did.

Q. May I see them, please?

A. Yes (handing). Those are the ones I brought.

Mr. HOFFMAN. Let the record show that Dr. Spaet has handed me ten documents, each consisting of several pages, some typed, some printed and some Xeroxed copies [5] of other documents.

Off the record, please.

(Discussion off the record.)

Mr. HOFFMAN. On the record, please.

Counsel for the defendants have agreed to dispense with reading the title of each of the documents brought by the witness. A list of those documents will be supplied to the reporter for marking as Exhibit 2 for identification.

Let the record also show that Mrs. Sisk has handed me four additional documents brought by her rather than the witness.

A list of those documents will be supplied and attached as Exhibit 3.

By Mr. HOFFMAN:

Q. Dr. Spaet, of the ten documents which you have brought with you, nine appear to be reprints of medical literature.

I wonder if you can tell us what they are, in general, and how they fit under the schedule?

A. These are two categories of paper. One is essentially a review of the literature and an editorial of evaluation of the bioflavenoids, and the other is the original papers reporting clinical results.

Q. By an evaluation of the bioflavenoids, are you [6] referring to a document headed "Drug Efficacy Study, Form A"?

A. No, I am referring to the report of the Council on Pharmacy and Chemistry of the American Medical Association.

That was in the way of an evaluation.

I am referring just merely—not to the ones that are the official forms that were given to us, but to the reprints.

Q. Is the report to the Council on Foods and Nutrition the one that was published in 1957?

A. Yes, it is.

Q. Can you tell us, Dr. Spaet, under what portion of the schedule these documents fell and why you brought them?

A. Well, it was my understanding, in interpreting the material, that any relevant material in our discussion today should be brought.

Q. What do you mean by "our discussion today," Doctor, so we have it on the record?

A. Well, I presumed we were going to discuss the FDA recommendation with respect to the bioflavenoids.

Q. When you received the subpoena, Dr. Spaet, did you personally search any files that are in your possession?

A. I did.

[7] Q. Are these all of the documents that you find in the files that you believe fell within the scope of the subpoena?

A. Yes, sir.

Q. I believe you mentioned, and it may have been during an off-the-record colloquy, that there were other documents relating to the products, other than those manufactured by USV Pharmaceutical Corporation, but that you did not bring those; is that correct?

A. That's correct.

Mrs. SISK. Those are the documents which I brought.

Mr. HOFFMAN. I see.

By Mr. HOFFMAN:

Q. Dr. Spaet, are you familiar with the documents produced by Mrs. Sisk?

A. Yes.

Q. Are those the only documents relating to the products of USV, which were in your files, to which you referred?

A. I would not be able to answer that without consulting my files.

Q. I wonder, Dr. Spaet, if you would check your files on that point and let me know in a letter the results of your further checking?

[8] A. Certainly. I think what you should do is provide me with some sort of reminder in writing.

Q. I certainly will. We will confirm this by letter after this deposition.

A. Thank you.

Q. Dr. Spaet, have you ever had other documents in your possession that fell within the scope of this subpoena, but which you do not have?

A. Yes.

Q. Could you describe those generally, please, and tell us also why you do not have them?

A. Yes, sir. In preparing our statement to the FDA we went through a certain amount of material, made notes, had a general statement of the material that we were to present, which we brought in in a rough form to meetings that we held, and these were not kept by us.

Q. These were notes of the meetings and notes of the thoughts of the panel members during this consideration of bioflavenoid products?

A. I did not—in my own possession—have notes of the meetings, but there was other material.

For example, we used as a basis for our decision—this is by no means an exhaustive list of it, it is just what I had in my file.

[9] Q. What happened to the rest of it?

A. I don't know. We left it at the buildings where the meetings were held. I don't remember the details.

Q. I thought you said, Doctor, there were some notes as to the meetings and notes as to the thoughts of the panel members. You say you did not have such notes in your possession at any time?

A. Well, can we go off the record a minute?

Mr. HOFFMAN. Sure. Off the record.

(Discussion off the record.)

Mr. HOFFMAN. On the record, please.

Q. Just to close up on this one subject, Dr. Spaet, who made the notes to which you have referred? Were they your notes or notes someone else made?

A. There are two categories of notes, notes I made myself and notes made by other panel members, including Dr. Middleman.

Q. Was he classified as a panel member?

A. He was executive secretary of the panel. He also made notes.

Q. But the notes you made were left on the table at the conclusion of the meetings?

A. Either that or destroyed in my own home or my own [10] office, which I think would be included.

Mr. HOFFMAN. Thank you, very much, Dr. Spaet.

Miss Levine will continue on related subjects.

By Miss LEVINE:

Q. Dr. Spaet, are you in private practice at all or is your time spent primarily in research?

A. If you say "at all," the answer has to be yes. I am in private practice to the extent that occasionally if a case that is particularly in my domain is brought to the attention of our staff, I will see such a patient, and occasionally I am called as an outside consultant, but this is a rare event.

Q. What proportion of your time would you say is spent in research?

A. In research?

Q. Teaching and private practice, each of those.

A. I would say half in research and the remainder in, let's say 30 percent in teaching and—

Q. So the private practice is small?

A. Negligible.

Q. Are you certified by a specialty board?

A. Yes.

Q. Would you state which one?

A. The Board of Internal Medicine.

[11] Q. Would you state what the specialty of hematology is?

A. Yes, it generally covers the blood and its disorders.

Do you want more detail?

Q. A little.

A. There are, I would say, four categories of hematology. One is the general problem of the white cell, one is the general problem of the red cell, and one is the general problem of the third type of blood cell called the platelet, and the fourth are the plasma proteins involved in blood coagulation.

Q. Does hematology concern itself with the structure function and the pathology of the vasculature?

A. That is a gray area, in the sense that I would say most hematologists have not been concerned with this but a few, and I would say a few of us have considered this an important component of hematology, since some of the blood components interact.

Q. What would that specialty be called that is confined specifically to the vasculature?

A. Let's go off the record.

Mr. HOFFMAN. Off the record, please.

(Discussion off the record.)

[12] Mr. HOFFMAN. On the record, please.

A. [Continuing.] You have raised an extremely complex question.

I have just finished writing a paper that I am going to present in a few weeks in Helsinki, in which the conclusions that this particular interaction between the hematology domain and the blood vessel is not as yet a discipline and that many people are doing isolated pieces of research in it, and it is high time they got together.

I think at this stage of the game the specialty of the blood vessel and the kind of reaction we are talking about is really not as yet defined.

Q. What is the nature of the research that you have conducted in medicine?

A. The general word that describes it is hemostasis.

Q. Would you describe that?

A. Hemostasis means the ability of the blood components that are responsible for stopping bleeding, the ability of these components to react normally and also abnormally.

On the one hand they don't work sufficiently so that bleeding results, and on the other hand they react inappropriately so that thrombosis results.

Q. Did any of this research that you have conducted concern itself with the vascular function of pathology?

[13] A. Yes.

Q. Can you say what that was?

A. Yes. In approximately 1950 I published my first major paper, which was entitled "Vascular Factor in the Pathogenesis of Hemorrhagic Syndromes."

I am quoting this title from memory of a paper I wrote some—almost twenty years ago.

The thrust of this paper was that when certain components of the hemostatic system, that is, platelets and blood coagulation are abnormal, the blood vessel suffers.

This is a concept which has been reviewed since 1959, and it is now the subject of the major work of the Thorndyke Laboratories.

Q. Have you carried out any further investigation in that area?

A. Our most recent area of interest is on the other side of the coin, as I mentioned. We are studying the type of disease that leads to thrombosis, the concept being that thrombosis is a blood vessel type of disease.

Q. Have you ever used CVP clinically or in any research?

A. No, I have not.

Q. Do you know if any member of the panel has used CVP in research or practice?

[14] A. I do not.

Q. Dr. Spaet, are you familiar with the guidelines that were set down for the panel on drugs used in hermatology disorders for all of the panel of the NASRC?

A. To the best of my memory.

Q. Would you describe generally what those guidelines covered?

A. Yes. It was our mission, as I read and understood it, that we were to ascertain whether a drug, first of all, was efficacious and, secondly, whether there was any toxicity associated with the use of this drug that outweighed its efficacy and, thirdly, whether in any combination the added ingredient contributed to the efficacy of the combination, and fourthly, in general, that the burden of establishing efficacy rested upon the people who were marketing the drug.

Q. Do you recall what criterion was applied in determining whether a particular product was considered effective?

A. Do you mean how we came about arriving at this decision?

Q. Yes.

A. Yes.

Q. In general.

A. In general, yes. In general the major literature [15] on the subject was covered by us and our own breakdown and experience were added to it to produce what I suppose might be considered a new ingredient.

In some cases—to clarify that a little bit, in some cases the value judgment might not have been in the original publication, but adding together a series of publications without value judgments, our professional judgment was made and then the source of our decision.

Q. There was a panel on cardiovascular diseases; was there not, Dr. Spaet?

A. As far as I know.

Q. Was there a panel on obstetrics and gynecology?

A. Is it my role to remember and list the panels?

Q. If you remember.

A. I seem to recall one.

Q. Do you know the reason why the bioflavenoids were assigned to the panel on hematology and not the panel on obstetrics or gynecology?

A. The reason was not explained to us.

Q. Would you define the bioflavenoids?

What is a bioflavenoid?

A. Yes. The original of bioflavenoids, the original way they were identified as a group to be studied was that it was found in genepicious surveys. At that time, if my [16] memory serves me right, Szent-Gyorgy obtained material that was particularly abundant in citrus fruit, which was thought to be an essential vitamin, then labeled Vitamin P.

Szent-Gyorgy's preparation was shown to contain a group of organic compounds, not one particular material, and I am not enough of a biochemist to go into their structural formulas.

In any event, these were essentially called the bioflavenoids, after doubt arose as to whether they represented a true vitamin.

Q. Are there chemical differences between bioflavenoid products?

A. I don't understand your question.

Q. For example, are there chemical differences between hesperidin and citrus flavenoid compounds?

A. I would think that each extraction procedure—but again, I would not try to qualify as an expert in this area—but, again, each manufacturing procedure would differ, so that each final product would be different.

Q. Do you know whether there are chemical differences between rutin and citrlus flavenoid compounds?

A. I would not care to comment on that.

Q. Do you know if there are chemical differences between quercetin and citrus flavenoid compounds?

[17] A. I don't know the definitive answer to that question.

Q. Do you know if there are physical differences between bioflavenoid products?

A. I know that some are soluble in water and some are insoluble.

Q. Are there biological differences between bio-products?

A. This is a question that can't be answered unless biological activity can be established.

Q. Do you know if that can be established in the case of any of the bioflavenoid chemicals?

A. I do not know as a fact if there is any activity on the part of any of the bioflavenoids.

Could I ask you a question at this point, Miss Levine, and that is, if there is any limitation to the area that this discussion can cover?

Q. I think your counsel will advise you about the limitation.

Generally, we are discussing the procedure which you followed as a member of the panel and the discussions that you engaged in.

Mr. HOFFMAN. Incidentally, I wonder if I could ask one question of Mrs. Sisk at this point, [18] and ask——

Mrs. SISK. Are counsel going to take this in tandem?

Mr. HOFFMAN. No. I was going to ask Mrs. Sisk whether you are Dr. Spaet's counsel?

Mrs. SISK. No, we are not.

Mr. HOFFMAN. You are representing only the defendants at this point?

Mrs. SISK. That's correct.

A. To repeat my question, whoever is qualified to answer it, is one of the areas of jurisdiction of this discussion the products of other companies?

Q. To the extent that the bioflavenoids generally relate to

the CVP compound, the specific product involved in this lawsuit, I believe there would be some mention.

A. But you are mentioning them by trade names and not by chemical names.

Q. I have not mentioned any other products by trade names.

A. One of the things that does not come out in a verbal discussion like this, I think when words are capitalized, and I think whenever a capitalized term comes along it should be so designated.

Q. Dr. Spaet, will you state for the record what CVP [19] is?

A. CVP is a proprietary—it is a product of a drug company that contains citrus bioflavenoid compounds, ascorbic acid and a compound known as menadione.

Q. Would you state what CVP without vitamin K consists of?

A. It consists of bioflavenoids and ascorbic acid.

Q. Would you know whether it contains any related phenolic acids?

A. I can only state what the company states is in it, since I have myself done no analytical studies on the product.

Q. Are you familiar with the Freedman-Merritt paper which was a USV study on the flavenoid fragmentation and biological activity of CVP?

A. Not off the top of my head.

The authors, again?

Q. Freedman, F-r-e-e-d-m-a-n Merritt.

A. How was the question put again?

Q. Are you familiar with that paper?

A. The answer is I don't remember having read it.

Q. Would you or do you know whether differences in solubility which you mentioned before, could influence the absorption and, therefore, the biological activity of some [20] of these biofiavenoid compounds?

A. If the question is "could," the answer is yes.

Q. Are you familiar with the paper on the biological activity of the flavenoid compound by Menkin?

A. Yes, I am.

Q. Would you not regard that as a demonstration of biological activity of the flavenoid compound?

A. To the best of my knowledge, the findings of Menkin have not been repeated by other investigators.

Q. Would you regard his paper as demonstrating that?

A. The only thing I can say with respect to that is that he made such a claim in his paper.

Q. Was it demonstrated to your satisfaction in that paper?

A. No.

Q. Why not?

A. Why not?

Q. Yes.

A. Well, by the same token that originally some of the Szent-Cyorgy original observations were later retracted.

It is frequently the case that a single paper will be published and for whatever reason, and the reasons may be many, the work cannot be repeated. Unless there is a body of literature which seems to represent a consensus [21] of opinion among qualified investigators of this type, it does not become an accepted thing in medical literature.

Q. Except for that paper itself, would you have any reason to doubt the validity of it?

A. If I had read it for the first time as a first paper, I would be inclined to go along with it, but in retrospect, since years have passed without confirmatory words, the paper, I think, takes on less significance.

Q. Dr. Spaet, in connection with the panel's review of the CVP products, would you state which products specifically were reviewed? Would you name them?

A. I certainly couldn't do that without the complete list.

Q. If I gave you the list perhaps you might indicate whether or not you recall that the review covered them.

A. It would be only, you know—it certainly wouldn't be something that I would be willing to testify to, but I presume it is a matter of record, is it not?

Q. Do you recall reviewing CVP capsules?

A. As separate from CVP syrup and CVP with vitamin K?

Q. Yes.

A. Yes.

Q. CVP with syrup?

A. Yes.

[22] Q. CVP with vitamin K syrup?

A. Yes.

Q. Duo-CVP capsules?

A. If it is on the list there the answer is yes. But it seems to me there are three items on the list, and I don't recall any product from the USV, other than the ones listed in NDA-9965.

Q. So you are not certain whether or not the panel reviewed duo-CVP capsules?

A. If duo-CVP capsules are not listed here, then I certainly am not certain we examined them.

Q. Bivam?

A. It is not familiar to me.

Q. Prednis-CVP?

A. I am not thoroughly familiar with that.

Q. Prednyl, are you familiar with that one?

A. No. Did we, in fact, review them?

Q. I am afraid I have to ask you that question.

A. Because I have no recollection of any product of these names, and some of them are sufficiently striking so that I would be surprised if I had encountered them and did not remember.

Q. Dr. Spaet, would you state how the Panel on Hematology was organized and what your role in it was?

[23] A. How it was organized?

Q. Yes.

A. I cannot testify as to how it was organized. I can only apply myself as to how the picture of it came to me.

I received—I don't remember whether it was a telephone call or a letter from, I believe—and, again, I wouldn't be certain of this—Dr. Trexler's office, asking if I would be willing to serve on such a panel, and the general mission of that panel was designated in this letter.

When I agreed to do so, I received a formal invitation to do it, and I attended the first meeting with the other members of the panel and the chairman, Dr. Crosby.

Q. What is Dr. Crosby's full name?

A. William Crosby.

Q. When was the first meeting of the panel, if you remember?

A. I don't remember. About three years ago.

Q. 1966?

A. Something like that.

Q. What was your role so far as the CVP products were concerned, in terms of the panel's work?

A. I was given this group of products as the primary reviewer.

[24] Q. You were given it by whom?

A. I am not certain as to who made the assignments. I think it was probably Dr. Crosby who decided who was to be the primary reviewer and who was to be the secondary reviewer, with each group of drugs that we considered.

Q. Was that appointment, so-called, done through a letter or the first meeting of the panel?

A. We each received a package of this sort of documents (indicating), about six inches high, in which a rubber band was around those that were assigned to us.

Q. Would you define what it means to be a primary reviewer?

A. Yes. The primary reviewer was the one who was expected to make the most critical survey of the clinical literature on the drug in question and then draw up a preliminary statement as to how this should be considered by the total committee.

There was also a secondary reviewer who was expected to make up a similar document.

Q. Who was the secondary reviewer on the CVP products?

A. I don't recall.

Q. What kind of document did you make up on your initial review?

A. It was a summary of the literature on the subject, [25] including the principles expressed in certain critical reviews on it, plus a recommendation as to the various categories of evaluation that were given to us to include in our final recommendation and references.

Q. Did you do that by yourself?

A. I don't understand your question.

Q. Did you undertake this primary review alone?

A. I don't understand the thrust of the question.

Q. Did you consult any other member of the panel before you submitted your first report?

A. No.

Q. Did you consult anyone else?

A. No.

Q. In short, you yourself reviewed the literature and called up with the recommendations?

A. That's right. And, of course, the secondary reviewer did the same.

Are you interested in knowing what the sequence of events were next?

Q. I would be.

A. All right. The statements that we made were then sent around to all members of the panel for comments, and then the comments were collated at a meeting that we had and which we all attended.

[26] So that the first aspect of it was done by mail, so that the other members of the panel would be prepared, and when they came—when the time came for discussion they would not be receiving any information cold, they would have an opportunity to check on some of the references if they wished and to add additional material from their own specialty or additional references if they might have wished to comment.

Then the panel then met and discussed any point of difference, and then a tentative second draft of the document was drawn up, which was again sent around to the entire panel for additional comments, and it was finalized sometimes at the next meeting or sometimes it took a couple of meetings.

Q. Dr. Spaet, could you confine your testimony to the CVP products specifically?

A. I don't remember specifically how they applied to the CVP products. I would be certainly willing to state that in addition to the remarks we made—the primary and secondary reviewer made—there were additional remarks made by other members of the panel, which I do not recall.

For example, one member of the panel referred to us a paper in which it was felt that some of the biological activity attributable to these was due to unsuspected [27] action of ascorbic acids.

Q. Dr. Spaet, specifically what did you evaluate in connection with your first review? Did you evaluate the materials submitted by the company?

A. Yes, we did.

Q. Did you evaluate the FDA file?

A. Yes, we did.

Q. Do you recall what material it was that was submitted by the company to you?

A. Yes, the company submitted essentially three things:

The photostat of the label, a photostat of the package insert, if I am not mistaken, and also a card that contained some additional material; and in addition to that, the company submitted a list of references.

Q. Biographical references?

A. Yes.

Q. What was the card?

A. The card contained indications other than those mentioned on the package itself.

Q. Was that a physician's file card?

A. Yes.

Q. Did you, in your consideration, look at any other material than that submitted by the company?

A. Yes, we did.

[28] Q. Would you state what that was?

A. Yes. We did a literature survey and read papers that were—that were other than those favorable to the product.

Q. When you say "we," Dr. Spaet, to whom are you referring?

A. The primary and secondary reviewer, and I presume other members of the panel.

Q. You are the primary reviewer?

A. I was, yes. Sometimes I am going to use the term "we" in the royal sense, so catch me up on it.

Q. Dr. Spaet, would you recall whether Dr. Frank Gardner was the secondary reviewer?

A. I would not recall specifically whether Dr. Frank Gardner was the secondary reviewer.

I would say that Dr. Frank Gardner is also active in the field of investigation of hemorrhagic disorders.

Q. If I were to read to you the other members of the panel, would you indicate whether any of the others were the secondary reviewer?

A. I can't make a statement.

Q. Do you recall whether Dr. Hugeley was?

A. No.

Q. Dr. Schilling?

[29] A. No.

Q. Dr. Zuelzer?

A. I do not.

Q. Dr. Spaet, you stated that you submitted to the panel after your review a statement or an evaluation; is that correct?

A. Yes.

Q. Can you tell us what the nature of that statement was?

A. I am repeating what I previously had said, if I am not mistaken, and I hope it corresponds fairly close to it. It consisted of the following:

A summary of the published findings of papers reporting results with these drugs, plus a summary of the conclusions we

reached by people who had reviewed the subject, plus an evaluation, according to the ground rules laid down on my own part, as to where I figured this group of drugs should be classified.

Q. And that was submitted to each member of the panel?

A. Yes.

Q. Where would that statement be at this time?

A. I have no idea.

Q. Did you keep a copy of it?

A. No, I did not.

[30] Q. Did you receive a copy of a report from the secondary reviewer, whoever he may be?

A. I did.

Q. Do you have a copy of that?

A. I do not.

Q. Do you recall whether his conclusions as evaluations were the same as yours?

A. They were.

Q. Did you ever refer the question of the effectiveness of CVP products to another panel?

A. I don't recall.

Q. To an outside consultant?

A. To an outside consultant, we did not.

Q. Incidentally, Dr. Spaet, did you or the panel——

You had no question, did you, about the safety of the product?

A. I would like you to clarify your question.

Q. Did you have any question whatever about the safety of these products when taken orally for the conditions represented?

A. You are raising, again, an extremely complex question and a yes or no answer would certainly not suffice.

Let me clarify my own feelings and, I think, the feelings of the panel, and if I am not mistaken, also the [31] guidelines laid down with respect to safety, as we understand them in terms of how the panel interpreted them.

If an individual has a disease that requires therapy and this therapy is delivered by administration of an inefficacious product, which is thought by physicians to be efficacious, from our point of view it meant that the agent was not safe.

If you are giving, for example, a placebo to treat a severe infection, even though this placebo in itself might not damage the patient, it was not safe.

Q. So as far as the safety or toxicity of these products per se——

A. I think there is a difference between safety and toxicity in this sense: You might say there is a category of reaction called pharmacological toxicity, in which an individual, a normal individual, given these agents would not develop adverse reactions.

In this sense, we did not consider that the bioflavenoids had that type of pharmacological toxicity.

On the other hand, if a patient had a bleeding disorder and a physician who was influenced by material on the subject gave it in place of definitive therapy, this would be unsafe.

Q. What definitive therapy would be recommended in [32] place of CVP?

A. For what condition?

Q. For abnormal menstrual bleeding?

A. Abnormal menstrual bleeding can occur on the basis of several different etiologies.

It is, for example, thought in 1969 that one source of abnormal menstrual bleeding is the administration of aspirin.

Removal of the aspirin would be the treatment in that case. This is an example.

There are many other possible causes of abnormal menstrual bleeding. For example, a woman will have abnormal menstrual bleeding if her blood platelet count is very low.

One example of appropriate treatment for that would be removal of the spleen.

Q. Dr. Spaet, in your consideration of these products, did you take into account their wide acceptance by many doctors and their accepted usage over the years? Was that a factor in your evaluation of these products?

A. It was not.

Q. It was not?

A. No.

Q. Would you explain why?

A. Yes. We feel that many inefficacious products are widely accepted.

[33] Miss LEVINE. May I suggest we take a five-minute break.

(Short recess taken.)

Miss LEVINE. On the record.

The WITNESS. I would like to say I was asked somewhere along the line whether we considered the original FDA file in reviewing this drug, and I answered yes to that. That is erroneous.

We had not gone over the original FDA file.

By Miss LEVINE:

Q. You reviewed only the Form A submission of the company?

A. Yes.

Q. And the literature that was cited there?

A. Not only the literature that was cited there; the literature that was cited and in addition, the literature we ourselves uncovered.

Q. Dr. Spaet, you stated that the literature which was cited by USV was unsatisfactory, I believe?

A. I did not say unsatisfactory, I said incomplete. I didn't say that, I implied it.

Q. Would you state why it was incomplete and what other literature you consulted in connection with your evaluation?

[34] A. The reason it was incomplete, of course, was that it only contained material favorable to the product.

Q. Aside from the fact it was favorable, what were the defects in it?

A. The defects in the papers cited by the Company were that they were unconvincing for the papers made for the efficacy of the drug. In addition to that were papers we obtained from various sources, but that they included negative studies and evaluations from other physicians who had done complete reviews of the world's literature on the subject.

Q. Why were the papers unconvincing?

A. I think this raises a question as to what it takes to create a convincing paper.

On the basis of criteria that I think most investigators would accept—first of all, the possibility of bias in any study has to be eliminated, and the way this is eliminated is to do essentially two maneuvers: First of all, one has to have a group of patients who are being treated with the presumably effective agent and a control group that is being identically treated, but just missing the active ingredient present in the others.

Secondly, neither the patient nor physician nor anyone else involved in evaluating the effect should be aware [35] of what is being given.

In other words, the general principal of a double-blind study. The patients should be randomized in such a way that there is no bias with respect as to who falls into which group, and none of the papers cited were anywheres close to that type of study.

Q. Were any of the other papers that you consulted based on that kind of study?

A. The closest to it was a paper published in 1944, that I have in my file here. This one (handing), by Rudy, Beaser and Seligman, and a group of papers—they were not done double-blind, but groups of controlled patients, with respect to the effectiveness of bioflavenoids in increased capillary fragility of diabetes mellitus.

Q. Do you know what specific product was used in that test?

A. Hesperidin, and the trade name of the product was Eriodictyol.

Q. What is Eriodictyol.

A. It is a proprietary preparation of bioflavenoids, available in 1944. I don't know if it still is available.

Q. But this test was done with hesperidin?

A. Yes.

[36] Q. And this was before CVP was in existence?

A. Yes.

Q. Were any of the other papers you consulted based on the kind of study you think is essential?

A. No, these studies seem to be unavailable with respect to a preparation of this sort.

Q. So the only studies you find which were satisfactory, was the Rudy, Beaser & Seligman study in 1944?

A. I don't recall any other studies—wait a minute. I would have to go back to my original files.

If memory serves, there were a couple of other double blind studies that were performed with negative results.

Q. Were any of them performed on CVP?

A. As far as I know, no, but I would not be sure of that.

I would like to add that any preparation containing ascorbic acid could have effects attributable to the ascorbic acids.

Q. Dr. Spaet, if you could look at your files and see whether any of those other studies were appropriate ones in your view, we would appreciate having that supplied to us.

A. Fair enough.

Would you again includes this in the letter you send me?

A. Yes.

[37] A. In reply to that, do you wish me to confine myself to CVP or any other bioflavenoid preparation?

Q. To the extent that your comment on CVP would take into consideration other bioflavenoid products, I think it would be relevant.

A. All right.

Q. Dr. Spaet, I show you the document under Log. No. 734, which you brought with you this morning in response to the subpoena, and ask you to look at the last page of this submission entitled "Reference."

Do you know whether the Jacob study was a double blind study of the kind to which you referred before?

A. The Jacob study I don't remember. I did not review that in detail for this session for the following reason:

Our panel was not dealing with the Rh problem, and this was not considered as a problem within the jurisdiction of the assignment given to us, that is, with respect to the bleeding.

Q. Would you define specifically what your assignment was?

A. Our assignment—

Q. In connection with CVP.

A. Yes, with respect to CVP. A problem arises, and [38] that is that we were not assigned the card which is Xeroxed here (handing), or we were not assigned the contents of the PDR Physician's Desk Reference.

Mr. HOFFMAN. Let the record show that Dr. Spaet has referred to a copy of Physician's File Card.

By Miss LEVINE:

Q. Would you specify what your assignment was?

A. Our assignment was only the package insert.

Q. Would you recall what the condition of use was?

A. Yes, it was stated that the package insert was—to the effect that these were supplementary sources of—supplementary vitamin sources or something to that effect.

Q. Do you have a copy of the package insert to which you are referring?

A. It is on there (indicating). The page before that. There it is (indicating).

It reads as a supplementary source of bioflavenoids, ascorbic acids——

Mr. HOFFMAN. Let the record show that the witness is referring to page 3 of the 7-page document which Dr. Spaet

brought with him today in response to the subpoena, designated Log 734 at the top.

Q. Dr. Spaet, when you say a package insert, are you or do you mean to refer to this written material on this [39] page?

A. I do.

Q. Did you not review any other material in addition to this page, in connection with CVP?

A. We did not. In connection with CVP, the answer is, we did not.

Q. Are you aware that that page incorporates three label statements from CVP?

A. I am.

Q. And that that is not the package insert?

A. What was given to the panel to review was done by the administrative components of the panel.

In other words, we were handed material, and from this we were to ascertain what the claims were.

Q. Dr. Spaet, would you, for the record, state what is contained as a condition of use for each of the products on that page, identifying the products?

A. Yes. CVP with vitamin K tablets.

It was advised that caution be used on the treatment of pregnant women.

Q. The condition of use. What was it recommended for?

A. As a supplement source of bioflavenoids, ascorbic acids and menadione, and the same applies to CVP with vitamin K tablets, capsules and syrup.

[40] Q. So I understand you to say that you did not review the package insert for this product which contained conditions of use under a prescription legend, but only the conditions listed on the labels which you have just read?

A. That is correct.

Q. Then there was no consideration of the CVP products in capillary fragility?

A. These specific products, no, but in other companies, preparations of bioflavenoids, there was.

Q. What was the reason you did not consider the package insert or the Physician's File Card which is listed in that document, Log No. 734?

A. Because the source of indications as presented to the panel lists was provided by the administrative component of the panel, and we only considered what was presented to us.

Q. Would you state what the administrative component of the panel was in this particular case?

A. Yes, there was an executive secretary who screened the material that came to us so that our job would be made easier, so that we wouldn't have to go shuffling through specific labels and package inserts and things of that sort, and he would ferret out of these that which we were to consider.

[41] Q. Would you state which products, which bioflavenoid products you did consider, in terms of conditions of use in bleeding disorders and the like?

The WITNESS. I would like to ask Mrs. Sisk if at this stage of the game we are going to discuss other products?

Mrs. SISK. It is all right.

A. Rutin was one, a product of Abbott Laboratories.

Ruterbin, a product of Squibb.

Q. Dr. Spaet, as you are referring to these would you designate the long number?

A. 798 in the case of Rutin, 1997 in the case of Rutorbin, and 2407 in the case of Rutin made by Parke-Davis.

1504 in the case of quercetin of Abbott Laboratories.

Q. Then your evaluation, again, Dr. Spaet, was confined to CVP as a supplementary source of bioflavenoids?

A. That's correct.

Q. And you did not give any consideration to the effectiveness of CVP in capillary bleeding?

A. Not in the evaluation we submitted.

Q. In habitual or threatened bleeding?

A. Yes.

Q. And normal menstrual bleeding?

A. That's correct.

[42] Q. Gingival bleeding, non-thrombocytopenic or in strengthening the placental capillary barrier against escape of fetal red blood cells into the maternal circulation?

A. That's correct.

Q. Dr. Spaet, we will go back for a minute to the question of biological activity.

A. Yes, ma'am.

Q. Do you know whether there is pharmacologic evidence of the specific activity of the citrus flavenoid compound which is incorporated in CVP?

A. I pass.

Q. What would your answer be, Dr. Spaet?

A. My answer would be I am not aware of specific evidence—of the specific convincing evidence of pharmacological—well, pharmacological activity has been claimed for the citrus bioflavenoid compound found in this preparation.

I am not prepared to evaluate it at this point.

Q. Are you familiar with Lung Proteolysis, published by Ungar?

Miss LEVINE. Off the record.

(Discussion off the record.)

A. Then I am not familiar with the particular studies.

Q. Are you familiar with the anti-genic serum test?

[43] A. I am not.

Q. Are you familiar with other anti-inflammatory test procedures which are believed to involve capillary or collecting venules?

A. I am familiar with such a test, however, I am not familiar with how they have been applied to this particular group of compounds.

Q. Do you know whether the citrus flavenoid compound which is incorporated into CVP is active in all of these tests?

A. I do not. I would like to, however, add that our assignment was not to ascertain whether or not biological activity could be demonstrated in animals, but whether these agents had chemical efficacy.

I will state we did not review the animal literature with the same kind of diligence that we reviewed the human disease literature, and there are, of course, many reasons for this.

Our assignment was clinical efficiency. We were not concerned with what drugs the rats might purchase.

Q. Dr. Spaet, did you ever see the supplemental submission which the USV Company made to the FDA, dated February 15, 1968?

A. I did not. To my memory, I did not.

[44] Q. Do you know whether any member of the panel ever saw that submission?

A. I do not know.

Q. Did you ever see the paper written by Dr. E. M. Clayton, entitled "Effective Citrus Bioflavenoid Carbazochrome Salicylate and Ascorbic Acids on the Transplacental Passage of Fetal Erythrocytes," which was published in 1967, in the journal of Obstetrics and Gynecology?

A. No. I would like to add, however, that this particular reaction would not have come under the jurisdiction of our scope in any case, because our assignment was with respect to bleeding and the transplacental passage of cells is on the basis which has not been fully established. I am not sure that this entire subject would have been appropriate for the Hematological Panel.

Q. What panel would it be appropriate for?

A. I suspect the Obstetrical Panel, but that is just a suspicion.

Q. Did you ever see the report by Dr. Milton Gotlib, entitled "Clinical Evaluation of the Role of Duo-CVP in Menometrorrhagin Associated with I.U.C.D."?

A. I don't recall that publication.

Q. So that neither of these papers was taken into account in the panel's evaluation of CVP?

[45] A. I don't recall that they were.

Q. And neither was taken into account in the evaluation of any of the other bioflavenoid products?

A. Well, they wouldn't have been appropriate for other bioflavenoid products, since this contains ascorbic acids, and the pharmacological activity of flavenoids would have had to have been separated out. under separate circumstances.

Q. Would the review of that paper, from the title, have been appropriate for the panel on hematology?

A. I think not. Menometrorrhagia is sometimes, but usually not a hematologic disorder.

Q. Was there something else you wanted to add?

A. Me?

Q. Yes.

A. No.

Q. You said it would have more appropriately been referred to another panel?

A. The referral to other panels was not my decision.

I think it probably was a mistake I made a suggestion of referring a drug to another panel previously, and I think that my remarks should be stricken from the record.

Q. We will take your comment into account, but we won't strike it.

[46] A. Okay.

Q. Are you familiar with Clemetsen's work on the presence of the oxydation of ascorbic biofiavenoids in humans?

A. I have heard of the work, but I am not familiar with it.

Q. I gather this paper was not taken into account in your evaluation?

A. Well, it was taken into account in the sense that we considered the possibility that this might be a useful action of the drug, but did not feel it was adequate for the claims made for it.

Q. Which claim are you referring to?

A. The claim that it has a separate effect of ascorbic acids on blood vessel integrity. I am not talking about CVP, I am talking about bioflavenoid integrity.

If the blood prolongs the action of ascorbic acid, then the presence of adequate amounts aof ascorbic acids would not be improved upon.

Q. Dr. Spaet, in the report on CVP which was submitted by the panel, the citation which appears on the bottom of that document is to Byrnes.

Was the Byrnes evaluation based on the kind of double blind clinical study to which you previously referred?

[47] A. No, it was not. The Byrnes evaluation was a section in the chapter of the standard textbook of pharmacology, Goodman & Gilman, which is the Bible in its field.

What Byrnes has done in this case is something similar to what the panel did, that is, evaluate the literature and came to a conclusion.

Byrnes was not used as the source of information, but was used as a statement from an authoritative individual that agreed with our own, I would say for sake of economy, for citation.

There has been earlier papers in which the establishment of the bioflavenoids as a vitamin had been discounted.

Q. Do you recall whether the Byrnes review of the bioflavenoids as a vitamin had been discounted.

Q. Do you recall whether the Byrnes review of the bioflavenoids referred specifically to studies using CVP?

A. I don't recall that it did.

Q. So that Byrnes' comments were based on studies involving rutin or hesperidin, other bioflavenoids?

A. Yes.

Q. Other bioflavenoids than CVP?

A. I don't know without referring back to Byrnes.

Q. Would this be true also of the comment by Yaconna, which is the other study to which the panel referred?

A. I think it would.

Q. To what extent was the evaluation of "ineffective" [48] based on—had it been the informed judgment of the panel?

A. How do you quantitate that?

Q. I believe this is a criterion that was mentioned in the NASNRC report itself.

A. Well, I think that in the last analysis the evaluation is 100 per cent of informed judgment of the panel. The conclusion derived by the panel from all of the evidence presented to them. The panel has not in any of these cases, except coincidentally, done original research in the areas under discussion, so that what they are doing is evaluating the literature and adding to it their own background in the field.

Q. Dr. Spaet, in the case of CVP, would you state for the record the exact nature of the—the exact procedure that was followed by you in making the evaluation and referring it to the panel? You mentioned it generally before, I believe.

A. Yes. I don't recall the exact procedure in the case of the CVP.

I would not be able to dissect out of the various bioflavenoid preparations the exact procedure for each separate one.

Q. You evaluate all of the products together, all of the bioflavenoid products?

[49] A. In going through the literature, this is obviously what had to be done.

In evaluating the specific claims made by each product, this was done individually, based upon the wordings of the claims, which were different in each case.

Q. Was that done by you?

A. It was done to a certain extent by me and to a certain extent with the collaboration of the panel.

In other words, the panel would sit down and say to each other, there is a difference between this claim and that, although it sounds similar, for example. But the details of how it applied to CVP are lost to my memory.

Q. You made an evaluation incorporated in a document which was circulated to all members in a panel, which was before a panel meeting?

A. Specifically with CVP?

Q. Yes.

A. I don't recall that was the case.

Q. Generally with the bioflavenoids?

A. Yes, generally with bioflavenoids. Specifically with CVP, I don't recall that.

Q. Do you recall at which panel meetings CVP was used?

A. No, I cannot.

Q. Do you recall any panel meetings that were devoted [50] to a discussion of CVP or the bioflavenoids?

A. I do not.

Q. How was the report which appeared on page 5 of the 7-page submission under Log No. 734, how was that report compiled and drafted?

A. Well, again a preliminary copy of this, as applied to claims, was written up by—specifically whom, I don't know. In the first case, I don't recall whether I did or Dr. Middleman did. And this was then circulated to all panel members for comment, and then at a meeting of the panel the pile of the drawings that we were considering at that particular meeting was set in front of us, and we went through them one at a time for any further corrections or comments.

A final copy was compiled, and based on that it was sent to the panel for approval, and if there was no comment, it went to the FDA.

Q. This was generally on bioflavenoids?

A. This applies specifically to CVP. That is, every member of the panel saw every report of the sort you are seeing here and had the opportunity to comment as he saw fit.

Miss LEVINE. Off the record.

(Discussion off the record.)

(Whereupon, at 12:05 p.m. a luncheon recess was taken.)

[51] AFTERNOON SESSION 1:20 P.M.

[Theodore H. Spaet, the witness, resumed and testified further as follows:]

Examination (Continued) by Miss LEVINE:

Q. Dr. Spaet, you testified, I believe, that the panel had evaluated CVP with respect to its usefulness as a supplementary source to bioflavenoids only?

A. Yes.

Q. What was the reason that you were consulting the literature relating to capillary fragility which had been supplied by the Company on Form A?

A. Well, this was a source of reference that was used for some of the other agents, and there was, of course, some overlap. But when the final evaluation came out on CVP, we did not know that this was going to be the single consideration.

When we got bioflavenoid preparations, we assumed that in general, since they are used for bleeding disorders, that they would all include that, so that in the process of searching the literature I used what I anticipated would probably come up.

Q. Is it valid to equate all bioflavenoids with respect to efficacy for all conditions of use that are repre [52] sented in the labeling?

A. Probably not.

Q. Would you explain that?

A. Well, if there were a single compound involved, such as, for example, aspirin, as an identified chemical compound, then a statement that applied to one preparation of it could apply to all in equal manner and equal degree.

On the other hand, when you are dealing with a group of compounds with undetermined differences in the method of extraction, and undetermined differences between the ratio of one and the other, and perhaps a single member of the group, under the circumstances then a statement cannot be universally applied as they could be with a single compound.

This is a hypothetical question, of course, because if there were a question of efficicacy in one, and one tried to bring it to the other, under the circumstances it would arise as to whether they were the same compounds. If no one of the group contained an efficacious material, it wouldn't matter what the variation might be from one to the other.

I would give an example in this case of, say, mineral water in the treatment of bleeding disorders.

Mineral water has various compositions, but if there [53] is no evidence that any one mineral water works, one needn't be preoccupied with the differences between them.

Q. Would you apply the findings on efficacy that were made as to rutin to CVP?

A. Well, the problem in this case is that rutin is a preparation containing bioflavenoids only. CVP contains ascorbic acids. Obviously the ascorbic acid is going to have reactions not mani-

tested by rutin, so the statement could not be used interchangeably.

Q. Would you apply the findings on rutin to the citrus flavonoid compounds of CVP?

A. Well, I would apply the findings by any publications supporting efficacy of a product only to that material if there were efficacy.

In the absence of efficacy, then there is no evidence that the drug is efficacious and there is nothing to apply.

Q. In this case, Dr. Spaet, there were findings as to the lack of efficacy of rutin for any condition.

A. Excuse me. It was the lack of findings for efficacy, not the lack of efficacy that we are concerned with.

In other words, there is no study that demonstrated beyond a reasonable doubt that these agents are inefficacious. As I mentioned earlier, our guidelines were that [54] the burden of proof rested on the company supplying the copy. It rested on them to demonstate that their product was efficacious, and in none of these cases was there any such a demonstration, in any form, in any combination, with respect to the bioflavenoids or with respect to any other possible member of the group.

Q. But the failure of the copy which you found to make a showing of efficacy of rutin, could that be applicable to CVP?

A. No, it could not. CVP has its own failure to show efficacy.

Q. For what use did you find, doctor?

A. Well, the use that we applied ourselves to in this particular report is the only one I can make a statement about, and as we stated, since there is no established requirement for the components of this drug, then its inclusion did not demonstrate efficacy.

Q. In discussing Menkin's paper, you referred to the need for a consensus of qualified investigators, if a finding is to be accepted as part of scientific knowledge.

A. Yes, it is to be incorporated into the body of scientific knowledge, right.

Q. Is that the standard you used in reviewing CVP?

A. We are dealing with two different subjects. [55] Menkin's studies were animal work.

In CVP, we are concerned basically with the efficacy of this study, whether Menkin's work would be applicable would be a completely different question—

Q. I think you misunderstood the question. It was a question as to whether or not the standard you applied in reviewing the product was that of the consensus of qualified investigators.

A. Let me rephrase the question and see if this is what you intend, before I answer.

Q. I would be delighted.

A. Do you mean if I were to head a group of hematologists, whose particular excellence was the bleeding disorders, that they would accept the kind of studies that are published in support of CVP?

If that is not your question, then I don't understand your question whatsoever.

Q. You are not reviewing CVP with respect to bleeding disorders.

A. That's right, but you asked me a hypothetical question.

Q. I asked you what standards you applied.

A. In this particular case, the standards we applied were, did the package insert have a statement which efficacy [56] would correspond to it.

And the prevailing opinion at that time, in 1965, was that there is no established vtiamin P. The body of expert opinion on this is that there is no vitamin P. Accordingly, the use of vitamin P as a vitamin would not be an efficacious step.

Q. Was the standard the body of expert opinion?

A. The standard in this particular case was the conclusion as determined by two components: one was a withdrawal of the original concept as enunciated in the first place by Szent-Gyorgy. He went back on his concept that vitamin P was a vitamin.

Number two, that the authoritative documents, such as Goodman and Gilman in 1959 and '66, did not consider P to be a vitamin.

These are the two types of opinions on the subject.

Mr. HOFFMAN. Off the record.

(Discussion off the record.)

Miss LEVINE. On the record.

By Miss LEVINE:

Q. In coming to the conclusion that CVP products were ineffective, what were the standards or the criterion that you applied in reaching that conclusion?

A. I think the answer to that question, as I see it, [57] breaks down into two parts.

The first is the general principle that if a component of a preparation is inefficacious, then the use of that component in a mixture is an inefficacious step.

The next question that comes up is why this component is inefficacious itself as a vitamin supplement.

Q. What I am asking you is whether or not you based your conclusion on a consensus of qualified investigators or the lack of a consensus of qualified investigators.

A. Oh, well, the—it would be the lack of consensus, I would say, for this reason: that there was not a group of qualified investigators who did the studies, that demonstrated that so-called vitamin P was not a vitamin.

There was no body of evidence collected into one review in which many negative studies were collected. It is the lack of confirmatory evidence that a deficiency state existed as to this group of material, which could be corrected in the way a classical vitamin deficiency is corrected.

There was no further body of confirmatory evidence along with reversal of the convictions of some of the investigators who originally held these opinions.

Now, again I think we are probably tied up a little bit on the problem as to what constitutes a body, now [58] many members have to be present to constitute a body.

I know a minion, but a body is not clear to me.

Q. Dr. Spaet, under the standard which you applied, if there was a substantial amount of well-documented favorable evidence, but if some of the evidence were not conclusive, would that preclude a finding of effectiveness?

A. If there were a body of favorable evidence, of course we would have a different viewpoint, a body of favorable evidence that fulfilled the criteria I outlined earlier. Of course the presence of bad studies does not mean good studies could not come along.

I think the same situation prevails here as prevails with flying saucers, that there is a large body of evidence that has been presented, and the people who have considered flying saucers say if we see a good study on the flying saucer we will accept it.

Q. We are in a little different realm here with CVP.

A. Explain that to me.

Q. During any of the panel meetings, did any panel members express the opinion that CVP should be placed in the possibly-

effective category rather than in the ineffective or any condition category?

A. Never.

Q. Any biflavonoid product?

[59] A. Never.

Q. You mentioned that the Beaser study in 1944 was one of the literature references which you considered unfavorable to the bioflavenoids generally, though it did not specifically deal with CVP?

A. Yes.

Q. Would you list the other unfavorable literature references on which you relied for your evaluation of CVP?

A. Well, I would have to give you one or two off the top of my head.

In Quick's Textbook of Hemorrhagic Disorders he mentioned that some investigators have used this in the treatment of hereditary hemorrhagic telangiectasia. Quick mentioned that he had no satisfactory results in attempting to duplicate these findings.

Q. Was this a controlled study?

A. No, he just states—this is one that sticks out in my mind.

Controlled studies of this sort, as I mentioned earlier I do not have with me but I will, if I can dig them up, send them in in a letter I am apparently going to send to you.

Q. Have you completed the literature references that you were thinking of?

[60] A. Yes. I thought rather than talk off the top of my head I should get back to more solid evidence.

Q. Were any of the unfavorable references cited in the panel's report?

A. The panel's report cited only summary papers.

Q. It did not cite any of the—

A. It did not cite the original work, that's right. It cited, as you know, the paper by Byrnes and the one by Yaomins, and I could not know if some of the other products there were additional references specifically cited, but it was felt that these would give a summary opinion rather than go back to specific individual papers, that this would be sufficient for the purposes of presenting our viewpoint.

Q. When you say it was felt, by whom was it felt?

A. By the panel.

Q. By Dr. Crosby?

A. No, the panel. All decisions that were made were group decisions.

Q. Was that placed on your recommendation?

A. As to which references should be used?

Q. Yes.

A. I don't remember how that specific designation came up. I don't remember also whether there were any [61] guidelines given to us as to how extensive our citation of the literature should be in documenting the decision.

I don't know that the guidelines were specific about that.

Q. If there were substantial pharmacologic evidence of biological activity of citrus flavenoid compounds and you were aware of it, would the clinical evidence be reviewed in a different light?

A. You mean if there were convincing evidence that the bioflavenoids—I am trying to rephrase your question so that it is clear to me.

If there were convincing evidence that the bioflavenoids had an antihemorrhagic effect in animals, would we have looked at the data differently; was that your question?

Q. Specifically with respect to CVP.

To clarify it, its pharmacological activity which would underlie the effect on bleeding disorders.

A. Well, what I do wish could happen is that Dr. Sadow and I would do this directly, because this would clearly cut through a lot of ice. Is it possible——

Q. No. I think the question should be answered.

Dr. SADOW. You and I will have to sit down one day and talk separately.

A. The question, if I understand it, if there were [62] some convincing evidence that there might be some possible relationship between this and blood vessel function in animals, would I have taken a different view to the clinical studies that we looked at; is that right?

Q. I was talking about the citrus flavenoids compounds.

A. Now there has been—I will maybe try to help you a little.

There has been some claim made in the literature that citrus bioflavenoid compounds have an effect on maintaining the material ground substantial. Ground substantial is a nonspecific term.

I think most people working in the field would prefer to use the term mucopolysachrites.

The question you are trying to ask me is if it could be conclusively demonstrated that mucopolysachrite integrity would somehow be influenced favorably by administration of bioflavenoids, would this alter my viewpoint with respect to the clinical study.

Q. I don't think that was the question.

Mr. HOFFMAN. Off the record.

(Discussion off the record.)

[63] A. No matter what animal studies show, if clinical studies are unsuitable, then efficacy is not demonstrated and no animal orientation is permitted to help.

Did that cut the knot?

By Miss LEVINE:

Q. Referring to the literature references attached to Form A, was the Carvel study, Part 2, a double blind study?

A. The Carvel study stated as follows:

If I am not mistaken——

Q. Was it a double blind study?

A. My answer, I think, will make this clear. A double blind study was attempted but it—I think this was the one—but it was clear that the physician could tell the differences on the basis of odor or something of that sort which were the placebo or which were the so-called active medication, so that a so-called double blind study was not actually performed.

There is one of the papers in which a double blind study was considered. Is that it (indicating)?

Dr. SADOW. No, that is not the one.

A. [Continuing.] If it is not that one, I would have to review. But the problem with that study was that he specifically states that the patients were suffering from malnutrition, and any correction in this study could have [64] been the correction of scurvy.

Q. Is the Carvel study the one that you brought with you, Doctor?

A. Yes.

Q. Can you establish whether that was a double blind study?

A. The whole study surely wasn't. Seven patients took part in the double blind study.

Let me read from this.

Q. Not at the moment, Dr. Spaet.

Was the Beaser study of 1944 a single blind study with Eriodictyol?

A. Yes, it was.

Q. Do you accept the results of that study?

A. Well, the point in this study is the differences were not shown.

Q. It was a single blind study?

A. Yes, it was.

Q. Was the company study which is cited in that submission a single blind or double blind study?

A. Company?

Q. On functional menorrhagia?

A. I don't know that.

Q. Was the Clemetsen study a single blind study?

[65] A. Yes, it was a single blind.

Q. This related to duo-CVP as against lactus placebo?

Mr. HOFFMAN. Off the record.

(Discussion off the record.)

Mr. HOFFMAN. On the record.

Can you repeat what you just said to me?

The WITNESS. I was informed if the answers that were requested from counsel did not give a clear view of my opinion, that I would be given the opportunity to elaborate on them.

Mr. HOFFMAN. Without getting into, right now, the question of who informed you, we would like to inform you that, if your answer conveyed the sense of the answer to the question that was asked, your answer will stand.

Only if you feel that the answer is not an answer to the question as you would like to state it——

The WITNESS. Are you stating that additional matter cannot be volunteered?

Mr. HOFFMAN. If it is not in response to a particular question, it cannot be.

Mrs. SISK. It can be if it is part of the answer.

The WITNESS. How is it ascertained that it [66] is part of the answer?

Mrs. SISK. If Dr. Spaet wishes to say something in addition to his answer, so his answer will be clear, of course Dr. Spaet may be able to do so.

Mr. HOFFMAN. The question was whether it was a double blind study, and it calls for a yes or no answer.

A. In the case of Carvel, it is true that a double blind study was done, but the double blind study did not relate in any way to bioflavenoids.

The patients were stated specifically as suffering from debilitating diseases.

I don't think anyone in the FDA or out of it is going to argue that ascorbic acids can improve persons with scurvy.

Also, it might be added that a double blind study in itself is not adequate to establish an observation.

A double blind study has to be done with adequate controlled patient selection and adequate evaluation of the data.

I think that in this study that clearly what Carvel and associates are dealing with is vitamin C deficiency.

Q. You are not excluding single blind studies as being acceptable?

[67] A. They may be acceptable, but I think that each single blind study has to be evaluated in its own right.

Q. Getting back to Clemetsen's study, did it employ an objective test procedure as a further measure of clinical response?

A. The answer as to the objectivity of capillary fragility studies is not as clear cut as Clemetsen would have you believe.

I refer you to the statement made by——

The WITNESS. May I have that file over there?

Mr. HOFFMAN. Yes (handing).

A. [Continuing.] Somebody did some studies, and I believe it is back to our old friend again in the archives in 1944. I believe it is a completely satisfactory method, even in 1966, if the——

Q. Do you know the method?

A. Yes. They used a negative pressure method. There were many problems with it.

Q. Doctor, how can you do a double blind study on threatened abortion?

A. Well, if you would like me to set up a study, I would be glad to do it for you.

Q. Would you describe——

A. In general how one might do it?

[68] Q. Yes.

A. Yes. What one would do is to randomly select women who are pregnant. That is, you take all women who are pregnant who show the following sign: A certain age of pregnancy. And then in a group of cards that are shuffled up, completely at random fashion, assign them to Group A or Group B.

The women you select would not be all pregnant women, but ones who have certain criteria for threatened abortion, which

I could apply myself to superefficiency, but I would have a group of gynecologists and obstetricians lay down as to which patients should be selected from this group.

These women are completely randomized, so that no bias can creep in.

Then what you would do, according to their cards, give them either a compound you are testing or a placebo that differs from the compound you are testing only in the absence of the ingredient you are testing. The personal administration of the material, the person taking it, the person evaluating results should not know which group the patient is in, and then whether those women go on to a full pregnancy or not should be ascertained by techniques used by people qualified in the field.

The data should be collected until such time as a [69] sufficiently large sample is established to ascertain the significance of it, and it should be written up and reported in a suitable medical publication.

Q. But there would be a risk that the woman on the placebo would abort?

A. There would be a risk that the women on active ingredients would abort, of course, and the reason you are doing this double blind study is because you want to know the answer.

There are double blind studies being done all the time.

Q. Would obstetricians generally want to take a study of this kind?

A. They would generally not, because they are busy, they are not scientists—we have had all kinds of pressure put on us when we have had studies of this sort—you read Arrowsmith.

Do you remember how it turned out when the wife got sick? She was not randomized.

So it is simply difficult to set up such studies.

The WITNESS. Off the record?

Miss LEVINE. Off the record.

(Discussion off the record.)

A. [Continuing.] I don't think that it is impossible to set up such a study.

[70] I should like to add for the record, that the study of Clemetsen that we have just been discussing, also is one in which the possible effect of those being tested is ascorbic acid.

Miss Levine, how can you possibly go for a point to prove—I am trying to show you the difficulty you are confronted with. This is a preparation of vitamin C.

Q. When was the report, the panel report, finally approved on CVP?

A. The date I don't remember.

Q. Do you know approximately?

A. About a year and a half ago, I should think. But it is not an authoritative statement at all.

Q. Was this about the fall of 1967?

A. That would seem like a reasonable time.

I seem to remember having a January deadline in my mind, but I don't remember which January it was.

Q. Would it have been January of '68?

A. That sounds reasonable, yes.

Mr. HOFFMAN. Dr. Spaet, we have just a few more questions on a general subject which I propose to put to you, then I think you will be ready for cross-examination.

[71] By Mr. HOFFMAN:

Q. Did you ever, prior to the filing of your final report on CVP and on the other bioflavonoids, discuss the work of the panel or your proposed report with any official of the Food and Drug Administration?

A. You mean aside from members of the panel and the executive secretary?

Q. Yes.

A. No. All of the discussion that went on was through the chairman. In other words, we never spoke directly to other officials.

Q. Did you have any communications with the Food and Drug Administration during the pendency of your review of bioflavenoids?

A. They just sent us bulletins as to what happened with our activities.

Q. But you sent nothing forward to them?

A. No.

Q. Your answer then is that you never did discuss any aspect of the bioflavenoid review with anyone from the FDA?

A. Are you including the sequence of events after you first telephoned me?

Q. No, I am talking about prior to the time your [72] final report was filed.

A. No.

Q. Specifically, did you ever discuss the bioflavenoid matter prior to the filing of your final report with Dr. Ralph Smith of the Food and Drug Administration?

A. No.

Q. As you just mentioned, we have had a couple of conversations by telephone.

Do you remember a telephone conversation we had back—I guess it was—in July, the first time I called you?

A. Yes, I do, vividly.

Q. Why do you remember it so vividly?

A. Because I realized this was going to represent an activity on my part that was going to be of some consequence.

Q. After we spoke did you communicate with any official of the Food and Drug Administration?

A. I did.

Q. Who?

A. I first got in touch with Mr. Drexel, to find out what my next move should be.

Q. He was the Executive Director of the Drug Efficacy Study for the NAS, was he not?

A. Yes.

Q. What did he tell you?

[73] A. He put me in touch with Mr. Goodrich, who subsequently put me in touch with Mrs. Sisk.

Q. Did you discuss with Dr. Drexel or Mr. Drexel what you should do?

Let's back up a moment.

For the record, what did I ask you in our telephone conversation; do you remember?

A. You asked me to make a voluntary deposition on my own.

Q. By that do you mean consent to be interviewed by representatives of USV?

A. I think that is what you intended.

What the legal terminology in this case is, I have no idea.

Q. Did Mr. Drexel give you any advice as to what you should do in response to my request?

A. Mr. Drexel said I would be well-advised to refuse this interview.

Q. Did he give you any reason?

A. Well, he said, first of all, he suspected that I would never be subpoenaed, that by the time this came around that the whole thing would have been dismissed and that I would never be further bothered.

So this was one consideration.

[74] The second consideration is that I felt——

Q. I was asking what Mr. Drexel told you.

A. That is what he told me.

Anyhow, he advised me not to engage in the informal interview you suggested.

Q. What did you then do?

A. I called Mr. Goodrich.

Q. May I ask what he told you?

A. He said the case would probably be dismissed and I would probably not be subpoenaed, but in the event it was, they would give me any advice I required.

Q. Did Mr. Goodrich advise you not to talk to us informally?

A. By the time I got to Mr. Goodrich—I believe, although I am not certain about it—this was already a closed matter.

Q. What was already a closed matter?

A. That I had decided not to talk to you informally.

Q. My question was whether Mr. Goodrich advised you not to talk to us informally?

A. I don't remember.

Q. Why did you decide not to talk to us informally, Dr. Spaet?

A. I felt I should have along with me some legal [75] advice, representing the side of the Food and Drug Administration.

Q. Dr. Spaet, did you do anything prior to this deposition to prepare yourself on the matters you anticipated might be covered?

A. Prior to the deposition?

Q. Yes, prior to our meeting here today?

A. Yes, I did.

Q. May I ask you what that was?

A. Yes, I reviewed the material that I brought with me.

Q. Did you consult with anyone?

A. No. Aside from having telephone conversations with Mrs. Sisk and Mr. Goodrich, no.

Q. May I ask you who initiated those telephone conversations?

A. Well——

Q. How many were there generally, roughly?

A. There was a misunderstanding, I have to tell you.

When I was on vacation, on returning, I had a message that I was called by the Public Health Service.

It turned out that it was you who had called me.

Q. I would like to state that I have never held myself out as a representative of the Public Health Service [76] and I am not now holding myself out in that position.

A. My secretary thought you were Mr. Goodrich.

Q. I am flattered.

A. I promptly called Mr. Goodrich's office, of course, so they knew what was going on, and a conversation ensued relevant to what happened here, and then I also, of course, returned your telephone call.

Q. Prior to coming here today, Dr. Spaet, did you discuss the general nature of your testimony with Mr. Goodrich or Mrs. Sisk or anyone of their colleagues in the Food and Drug Administration?

A. I did.

Mr. HOFFMAN. I have no further questions.

You may cross-examine, Mrs. Sisk.

Mrs. SISK. I wonder if counsel would be agreeable to putting in as an exhibit to this deposition Dr. Spaet's Curriculum Venti Publications which he will supply?

Miss LEVINE. We will be glad to.

CROSS-EXAMINATION

By Mrs. SISK:

Q. Dr. Spaet, during the course of the deliberation of the Panel on Hematology and Drug Efficacy Study, was [77] there general discussion or consideration of the use of bioflavenoids in the treatment of bleeding states in man?

A. Yes, there was.

Q. During the course of this consideration, did you find any evidence of efficacy for any bleeding state in man?

A. No.

Q. Did the panel collectively find any evidence of the efficacy of any bioflavenoid for any bleeding state in man?

A. No, they did not. There was no disagreement among the panel.

Q. Dr. Spaet, I have here with me for identification as Defendants' Exhibit A to this deposition Xerox copies of the

relevant pages from the Physician's Desk Reference for 1961, 1962, 1965 and 1966, concerning the product CVP and duo-CVP.

Mrs. SISK. If counsel would like to look at them (handing).

(Xerox copies of relevant pages concerning the products CVP and duo-CVP from Physician's Desk Reference for the years 1961, 1962, 1965 and 1966 marked as Defendants' Exhibits A, B, C and D respectively as of this date.)

[78] By Mrs. SISK:

Q. I want to ask you a few quick questions in your role as an expert in hematology.

Dr. Spaet, do you consider CVP with vitamin K or duo-CVP with vitamin K a safe drug for use in bleeding or hypertension?

A. No, I do not.

Q. Do you consider the product duo-CVP with vitamin K for use as an effective drug in bleeding and hypertension?

A. No, I do not.

Q. Can you tell me, Dr. Spaet, whether or not it is the consensus of expert hematologists that CVP with vitamin K or duo-CVP with vitamin K is generally recognized as safe in the treatment for bleeding or hypertension?

A. They are not.

Q. Can you tell me whether or not, as an expert, you consider CVP with vitamin K or duo-CVP with or without vitamin K to be safe for use in the treatment of diabetes?

A. No, I do not.

Q. Is it your opinion that it is the consensus of opinion between hematologists that this is generally recognized as safe for treatment of diabetes?

A. They are not.

Q. Would your answer be the same for bleeding in [79] retinopathies?

A. Yes.

Q. For bleeding in purpura?

A. Yes.

Miss LEVINE. Would you identify that?

Mrs. SISK. 1961.

By Mrs. SISK:

Q. In threatened and habitual abortion?

A. No.

Q. Bleeding in radiation therapy?

A. Same answer.

Q. Bleeding gums?
A. Same answer.
Q. Bleeding in epastaxis?
A. The same answer.
Q. Bleeding in duodenal ulcer?
A. The same.
Q. And gastrointestinal bleeding?
A. The same.
Q. Will you tell me whether or not this was your opinion in 1961?
A. It was.
Q. Was it the considered opinion of medical men in 1961?[80]
A. It was definitely, among the people working in the field.
Q. How about in 1962?
A. The same.
Q. In 1960?
A. The same.
Q. Let us ask an additional condition, bleeding in menorrhagia?
A. The answer is the same.
Q. And is your testimony the same as to the consensus of opinion among experts?
A. Yes.
Q. Today?
A. Yes.
Q. In 1960?
A. Yes.
Q. 1961?
A. Yes.
Q. 1962?
A. Yes.

Mrs. SISK. I believe that is all the questions that the Government has.

Mr. HOFFMAN. We have a couple on redirect examination.

[81] REDIRECT EXAMINATION

By Miss LEVINE:

Q. Dr. Spaet, you testified a moment ago that the panel generally discussed the efficacy of bioflavenoids in bleeding states in man; is that correct?
A. Yes.
Q. Did the panel specifically discuss the effectiveness of citrus flavenoid compounds in bleeding states in man?
A. It did.

Q. Did the panel specifically discuss the efficacy of citrus flavenoid compound in the reduction of transplacental passage of fetal erythrocytes into the maternal circulation?

A. It did not.

Q. Did it specifically discuss the effect of citrus flavenoids in the reduction of the incidence of intermenstrual bleeding following insertion of intra-uterine contraceptive devices?

A. It did not.

Q. Dr. Spaet, you also testified a few moments ago as to your belief as to what was the consensus of hematology opinions on various matters at various times.

A. Yes.

[82] Q. Where and how did you obtain your knowledge as to what the consensus was?

A. The specific conditions that were noted have been the subject of management publications in large number, using various techniques of management.

Q. You mean patient management?

A. Yes, patient management, and the use of these materials is not a feature of the management. That is, in the authoritative papers on the subject nor in the papers published on the subject in national meetings, nor in the discussions of the subject at seminars and other international conferences in which publication does not emerge.

In other words, being in this field one has the opportunity to have one's ears to the ground as to what people are doing and things with respect to the management of different forms of hemorrhagic states, and if these were considered to be efficacious agents, they would be prominently noted by the major investigators in the field, and they are not.

Q. So it is the absence of reference to citrus flavenoid compound or to bioflavenoid otherwise in these publications, which leads you to the conclusion that the consensus does not recognize the safety and efficacy of these products?

[83] A. In part. Also informally when the bioflavenoids come up and they received a certain amount of publicity in the newspapers, when the FDA first announced the decision with respect to them, I think this must have been a year ago, there was some publicity on it.

Then a good deal of informal discussion on the newspaper reports took place, and one could easily see what the opinion was of people working in the field.

The bioflavenoids were mentioned by people in this field as the drugs in which the FDA was on its firmest ground. This was a direct comment.

Incidentally, one has an opportunity to sample crosses of opinion at national meetings, such as the Federated Society for Experimental Biology, held annually in Atlantic City, and also the meeting designated as the American Society for Clinical Investigation meetings, which brings people from all over the country together in one place. It is around-the-table conversation, which often gives you insight as to where people stand on various subjects.

Since it did receive a certain amount of publicity, this particular group of compounds were specifically discussed.

Q. The discussion you are talking about is discussion within the last year, arising from the FDA's action against [84] the bioflavenoids?

A. That's right.

Q. So it would not have told you anything on the state of consensus in 1962?

A. No. But in 1962 one also had the opportunity to see what was being said and what was new and useful in the management and in the field, in these serious conditions.

Q. The more recent specific statements related to efficacy, however, did they not?

A. Yes.

Q. Not to the safety of the products?

A. They are not unrelated.

Q. Other than the point you made earlier, to the effect that the use of an inefficacious drug you considered it unsafe, other than aspect of safety, these discussions did not relate to safety, did they?

A. Again, I would like to emphasize from a pharmacological viewpoint. I have not heard anybody say this would produce adverse reactions.

I would like to emphasize that the consideration of safety I gave earlier is not a minor one. We consider it a major consequence that a person who has a potentially dangerous situation has his definitive therapy postponed.

[85] Q. This theory would be inapplicable, would it not, in a case where there was no definitive therapy?

A. You never know that unless you investigate the patient.

Q. You mean you don't know whether there is a definitive therapy?

A. You don't know which category into which the patient falls.

Q. In the categories where there is no definitive therapy, however, this consideration is not applicable, is it?

A. There are two forms of therapy that can be efficacious. There is definitive therapy that clears it up finally and also therapy that helps. In other words, a person who has a bleeding disorder can be rendered less severe.

There is a whole spectrum. It is certainly possible that there are patients in the category, who if they got bioflavenoids instead of being properly investigated would not be harmed by it.

In any given patient, you don't know.

Q. If you were to know, however, if you were to determine that there was no definitive therapy or no clearly superior therapy, this consideration of safety would not [86] be applicable, would it?

A. That is true.

Q. Doctor, is it your view that any drug other than the drug of choice is an unsafe drug?

A. Let me rephrase it.

Any treatment other than the treatment of choice is an unsafe treatment, and drug is only a subdivision of this overall category, because therapy would not always be drug.

You people are drug-oriented, of course.

Q. We are not physicians, I regret.

A. If you were in a surgical group and you were to say drug, they would say "what is that?".

Q. Then you would like to broaden the statement to reflect your belief that any treatment which is not the treatment of choice is an unsafe treatment?

A. Yes.

Q. Dr. Spaet, in functional regular menorrhagia, what is the definitive therapy?

A. Well, there is no—let me start all over again. I don't presume. This is a gynecological problem. The situation would be if a gynecologist has a patient who has menorrhagia, he would frequently send such a patient to a hematologist to evaluate whether a hemorrhagic state [87] exists.

If a specific hemorrhagic state can be identified, then the specific therapy for that is undertaken.

On the other hand, if the hematologist can give a clean bill of health for his field, I cannot state how the gynecologist would handle this. It is not in my domain to testify to that.

Mr. HOFFMAN. Off the record.

(Discussion off the record.)

Mr. HOFFMAN. On the record. We have no further questions.

Mrs. SISK. The Government has no further questions.

(Whereupon, at 3:45 p.m. the deposition was concluded.)

Subscribed and sworn to before me this — day of ———— 1969.

[88] CERTIFICATE

STATE OF NEW YORK,
County of New York:

I, Charles Richer, a Shorthand Reporter and Commissioner of Deeds of the City of New York, do hereby certify:

That Theodore H. Spaet, the witness whose deposition is hereinbefore set forth, was duly sworn by me and that such deposition is a true copy of the testimony given by such witness.

I further certify that I am not related to any of the parties to this action by blood or marriage; and that I am in no way interested in the outcome of this matter.

In witness whereof, I have hereunto set my hand this 6th day of October, 1969.

CHARLES RICHER.

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EXHIBITS

	For ident.
Plaintiff's, 1: Subpoena dated August 28, 1969, addressed to Dr. Theodore H. Spaet, 23 Rectory Lane, Scarsdale, N.Y.	3
Defendants, A, B, C, and D: Xerox copies of relevant pages concerning the products CVP and duo-CVP from the Physician's Desk Reference for the years 1961, 1962, 1965 and 1966, respectively	77

EXCERPTS FROM TRANSCRIPT OF PROCEEDINGS IN DISTRICT COURT, OCTOBER 23, 1970 AND OCTOBER 26, 1970

[14] * * * * *

The COURT. I think you have done a good job so far and I hope you are as cooperative with the rest of it.

Give it to the Clerk, your draft copy. Let the Clerk mark it. Mark it Stipulation as read into the record.

Mr. HOFFMAN. And as modified by the agreements of Counsel.

The COURT. That is right. That is the one that—he will write it all up from there.

Mr. HOFFMAN. Fine.

Mr. EPSTEIN. Thank you, your Honor.

Mr. HOFFMAN. Thank you.

The COURT. I just want it marked Copy for [15] stipulation so that the Reporter will know what it is.

(The stipulation of facts follow:)

Plaintiff and defendants, for the purpose of this action only and without conceding the relevance or admissibility of the following facts, hereby stipulate and agree that:

1. Plaintiff is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business in the State of New York. Plaintiff manufactures and sells drugs in interstate commerce.

2. Plaintiff has manufactured and sold C.V.P. Capsules, C.V.P. Syrup, C.V.P. with Vitamin K Tablets, C.V.P. with Vitamin K Syrup, Duo-C.V.P. Capsules, Duo-C.V.P. with Vitamin K Tablets, Bivam, Prednyl and Prednis-C.V.P., a line of citrus bioflavonoid products, as shown in Exhibit A hereto.

3. The sales figures for C.V.P. products in 1970, based on figures to date and reliable projections to the end of the year are:

Duo-C.V.P. Capsules		13,550,000
Duo-C.V.P. with Vitamin K capsules		3,565,000
C.V.P. Capsules		10,200,000
C.V.P. Syrup	oz	2,909,396
C.V.P. with Vitamin K Syrup	oz	119,600
C.V.P. with Vitamin K Tablets		5,850,000

4. "Bioflavonoid" is defined in Dorland's illustrated Medical Dictionary, 2nd Edition, as follows: [16] "a generic term for a group of compounds which are widely distributed in plants and animals and which are concerned with maintenance of a normal state of the walls of small blood vessels."

5. Each C.V.P. Capsule or .5 cc. (Approximately 1 teaspoon)

of C.V.P. Syrup, provides 100 mg. of citrus flavonoid compound of 100 mg. of ascorbic acid (Vitamin C). Each capsule of Duo-C.V.P. provides double these amounts per dose. The dosage recommended in the labeling of C.V.P. capsules is from six to twelve capsules per day. The dosage recommended in the labeling of C.V.P. Syrup and Duo-C.V.P. Capsules provides the same level of bioflavonoids and ascorbic acid as recommended for C.V.P. Capsules. The total daily recommended dose of C.V.P. Capsules, C.V.P. Syrup and Duo C.V.P. provides between 600 and 1,200 mg. of citrus flavonoid compound.

6. Each C.V.P. with Vitamin K Capsule or .5 cc. (approximately 1 teaspoon) dose of C.V.P. with Vitamin K Syrup provides 100 mg. of citrus flavonoid compound, 100 mg. of ascorbic acid and 0.66 mg. menadione (Vitamin K). Each capsule of Duo-C.V.P. with Vitamin K Capsules provides 200 mg. of citrus flavonoid compound, 200 mg. of ascorbic acid and 1 mg. of menadione (Vitamin K). The daily dosage recommended in the labeling of C.V.P. with Vitamin K is from three to fifteen teaspoons or capsules. The daily dosage [17] recommended in the labeling of Duo-C.V.P. with Vitamin K is two to eight capsules. The total daily recommended dose of C.V.P. with Vitamin K capsule, C.V.P. with Vitamin K Syrup, and Duo-C.V.P. with Vitamin K Capsules provides between 300 and 1,600 mg. of citrus flavonoid compound.

7. The daily dose of three tablets recommended in the labeling of Bivam provides:

Citrus Bioflavonoid Compound	mg	100
Ascorbic Acid (C)	mg	100
Calcium Lactate	Gm	1
Ferrous Gluconate	mg	100
Vitamin A	U.S.P. Units	6000
Vitamin D	U.S.P. Units	600
Thiamin Mononitrate (B_1)	mg	3
Riboflavin (B_2)	mg	3
Pyridoxine HCl (B_6)	mg	3
Vitamin B_{12} (cobalamin conc.)	mcg	3
Niacinamide	mg	25
d, calcium Pantothenate	mg	5
Folic Acid	mg	015
Menadione (K)	mg	1
Vitamin E (dl, Alpha Tocopheryl Acetate)	Int. Unit	1
Magnesium	mg	3
Manganese	mg	1
Copper	mg	1
Zinc	mg	1
Molybdenum	mg	0.2
Iodine	mg	0.1
Cobalt	mg	0.1

8. Each capsule of Prednis-C.V.P. contains 4 mg. prednisolone (a steroid); 100 mg. citrus flavonoid compound, 100 mg. ascorbic acid; 100 mg. aluminum hydroxide; 100 mg. magnesium oxide. The adult dosage recommended in the labeling of Prednis C.V.P. is two to five capsules daily, providing 200 to 500 mg. of citrus flavonoid compound.

[18] 9. Plaintiff filed new drug applications (NDA's) with the Food and Drug Administration for the foregoing products and they were made effective as follows:

	Effective date
NDA 9965:	
CVP Capsules	Nov. 8, 1955
CVP Syrup	Do.
CVP with Vitamin K Syrup	Do.
(Supplement):	
CVP with Vitamin K Tablets	Jan. 19, 1956
Duo-CVP Capsules	
NDA 11474: Prednyl	Aug. 26, 1956
NDA 11475: Prednis-CVP	Aug. 26, 1956

10. No NDA was ever filed with respect to Duo-C.V.P. with Vitamin K Capsules or Bivam. These two products contain the identical citrus flavonoid compound present in plaintiff's other C.V.P. products.

11. On October 9, 1962, the above products, with the exception of Prednyl which was no longer marketed at that time, were commercially sold and used in the United States.

12. In 1950 in response to a letter inquiry of April 19, 1950, from James B. Redd (copy attached hereto as Exhibit B), FDA by letter of May 31, 1950 (copy attached as Exhibit C) took the position that a product of identical formulation to C.V.P. was not a "new drug" when represented as helpful in increased capillary fragility.

13. By letter of January 3, 1957, the Food and [19] Drug Administration communicated to plaintiff its opinion that Bivam was not a new drug when distributed under labeling recommending its use as a dietary supplement. A copy of this letter is attached hereto as Exhibit D.

* * * * *

15. By letter of April 19, 1961, the Food and Drug Administration communicated to plaintiff its opinion that Prednyl and Prednis-C.V.P. (combinations of CVP and a steroid) were not new drugs when distributed under the labeling provided for in NDA 11474 and NDA 11475, respectively, in the dosages set forth above, which recommended their use in the treatment

of capillary fragility and permeability. The citrus flavonoid compound in Prednyl and Prednis-C.V.P. is identical to the citrus flavonoid compound in plaintiff's other C.V.P products. A copy of this letter is attached hereto as Exhibit E.

[25] * * * * *

Mr. HOFFMAN. We would like him to admit that in December. 1957, FDA was not concerned about the safety, per se, of the C.V.P. products.

The COURT. He could not—I will tell him not to admit that because I do not know that it is relevant, whether they were or were not. How can he speak for FDA?

Next question.

I mean clearly that is a conclusion. He could not speak for them if he wanted to and bind the Government.

Mr. HOFFMAN. Your Honor, he was their counsel speaking for the Commissioner for FDA.

The COURT. That does not make any difference. I understand. But a lot of counsel do not know what their clients have in mind sometimes.

Mr. HOFFMAN. Your Honor, we respectfully except to that ruling.

The COURT. You may except to it, and I do not know—what relevance does it have on you whether they were interested in it in 1896 or 1957? What difference does it make?

Mr. HOFFMAN. Your Honor, it is our position that it was the business of the Food and Drug Administration in 1957 and has been since to determine among other things [26] whether there is substantial evidence or, for example, of safety of products.

The COURT. Wait a minute. You are arguing the case.

Mr. HOFFMAN. And that is expert opinion.

The COURT. Mr. Hoffman, you are arguing. I am sure he will stipulate if you want him to do that in 1957 the FDA had not in fact taken any affirmative action. Now, it does not make any difference why they had not done it.

They had not done it. Isn't that correct, Mr. Epstein?

Mr. EPSTEIN. That is correct, your Honor.

The COURT. All right. It is stipulated they did not do it. It does not make any difference why they did not do it. They took no action in 1957.

Mr. HOFFMAN. Your Honor, the other fact that we believe they have already stipulated to——

The COURT. Now you may argue what that means later.

All right.

Mr. HOFFMAN. Your Honor, the other fact that we think they have already agreed to and would like them to agree to now is that as stated in their previously filed documents on or before October 9, 1962, and at all times since it was and is generally recognized by experts qualified by [27] scientific training and experience to evaluate the safety of drugs that citrus flavonoid compounds, that is bioflavonoid, when used in the dosage recommended for Plaintiff's products are not pharmacologically toxic in that a normal individual given these agents would not develop adverse reactions.

The COURT. All right.

Are you willing to stipulate that in your opinion, whatever that means, that experts would so testify if they were called?

Mr. HOFFMAN. Are you addressing that to Mr. Epstein?

The COURT. Yes, I am addressing it to him.

Mr. HOFFMAN. Your Honor, the——

The COURT. Wait a minute. That is all that says.

Are you willing to admit that experts, if they were called, would so testify——

Mr. HOFFMAN. Your Honor, I am reading——

The COURT (continuing). They are non-toxic.

Mr. HOFFMAN. I am reading from their statement.

The COURT. It does not make any difference. I now want to know it.

Mr. EPSTEIN. Your Honor, may I have just a moment to confer with the Doctor?

[28] The COURT. Yes. If not, you may put a doctor on and let him testify and we will get to that real quick.

What you are stipulating is that experts would say that these citrus or bio—what do you call them?

Mr. HOFFMAN. Bioflavonoids, your Honor.

The COURT (continuing). Bioflavonoids are not toxic when used in accordance with your prescription or your labeling, whatever you call it.

Mr. HOFFMAN. That is what they said before.

The COURT. That does not make it a fact. It is just an expert opinion that would say that.

Mr. HOFFMAN. That is exactly right, your Honor, and it is the statement——

The COURT. Expert opinions unfortunately are not always correct.

Mr. HOFFMAN. It is the state of the expert opinion, not the underlying fact that is the issue in this case, your Honor.

Mr. EPSTEIN. Your Honor, my difficulty——

The COURT. Just tell me yes or no. I do not want any difficulty. I mean really I am going to get to this.

Mr. EPSTEIN. All right.

The COURT. Are you satisfied that if experts were called they would testify to that statement?

Mr. EPSTEIN. Yes, they would, your Honor.

[29] The COURT. All right.

Mr. EPSTEIN. We will so stipulate.

* * * * *

[76] * * *

Mr. EPSTEIN. The government calls as its first witness, your Honor, Dr. Theodore H. Spaet.

The COURT. Step forward, Doctor.

Whereupon,

Theodore H. Spaet was called as a witness, and having been first duly sworn, was examined and testified as follows:

* * * * *

[85] * * *

By Mr. EPSTEIN:

Q. What are bioflavonoids, Dr. Spaet?

A. Bioflavonoids are materials extracted, basically extracted from various vegetable material but mostly fruit skins.

The COURT. Mostly fruit skins?

The WITNESS. Citrus fruit skins, that is right. [86] There are special chemicals that emerge in the extraction procedure.

* * * * *

[89] * * * The COURT. First do you have the committee opinion?

Mr. EPSTEIN. Your Honor, I do not have the committee's written opinion.

The COURT. Then you can't offer it.

Mr. EPSTEIN. That is why I am asking him specifically of his own opinion.

The COURT. All right. If you have it I will let you offer it. But he doesn't have it, he says.

Mr. HOFFMAN. Objection, your Honor.

Mr. EPSTEIN. Well, may I say——

Mr. HOFFMAN. His opinion is not relevant, the opinion of any particular expert is not relevant. The only issue would be the state of the expert consensus, not Dr. Spaet's or any other particular individual.

The COURT. Objection is overruled. It again goes to the weight of it. He can give his own opinion.

By Mr. EPSTEIN:

Q. What is your opinion on the plaintiff's bioflavonoid drugs, your Honor,—a—Dr. Spaet?

A. In my opinion the bioflavonoids as produced by the plaintiff have no demonstrated value in the treatment of bleeding disorders.

[90] Q. Doctor, is that opinion concurred in by your colleagues who are also experts in the field of hematology?

A. To the best of my knowledge this is virtually a universal rule among the people who are generally classified as my colleagues in this area.

Q. Has that view been communicated to you in the forms of discussions with your—

The COURT. Let's get to the meat of it.

Mr. EPSTEIN. All right.

The COURT. How many other doctors roughly in your field have you discussed the plaintiff's drug in question with, roughly?

The WITNESS. Well, I couldn't name the number with whom I have discussed it. But——

The COURT. Say approximately,——

The WITNESS (continuing). Possibly——

The COURT (continuing). One, ten, twenty——

The WITNESS (continuing). Possibly ten.

The COURT. All right. And of those ten that you discussed it with them, did any of them, either disagree or expressly agree with the opinions that you said that it had no effect?

The WITNESS. No, your Honor.

The COURT. What did they do?

The WITNESS. Well, we generally laughed about it.

[91] The COURT. You just laughed?

The WITNESS. Yes.

The COURT. So they expressed no opinion?

The WITNESS. No, no. They agreed with me, sir.

The COURT. How did they agree with you? Did they say you are correct, or just laugh?

The WITNESS. No. They say that—they conveyed to me that I am correct. I don't remember their exact words, your Honor.

The COURT. You got the impression from them that they didn't disagree with your opinion?

The WITNESS. That they agreed with it most heartily, your Honor.

The COURT. All right. That is about 10.

Let's take it from there.

By Mr. EPSTEIN:

Q. Doctor, is it your opinion that the administration of the plaintiff's bioflavenoid products to a patient who may be evidencing the symptoms of habitual and threatened abortion is a safe modality for the treatment of that condition?

A. I do not.

Mr. HOFFMAN. Your Honor, I object to that question on the grounds that there has been no showing that any of plaintiff's products are recommended for the treatment of threatened abortion rather than for the treatment of [92] capillary fragility when it occurs.

The COURT. I will allow you to cross-examine him. He is an expert. You can show that he is talking about something that does not effect you. That is the purpose of cross-examination.

By Mr. EPSTEIN:

Q. Doctor, is it your opoinion that the administration of plaintiffs' products to a patient who is suffering from postpartum bleeding is a safe modality for the treatment of that condition?

Mr. HOFFMAN. Same objection, your Honor.

The COURT. Objection is overruled.

The WITNESS. May I give my answer?

The COURT. Sure.

The WITNESS. I think it is not safe, your Honor.

By Mr. EPSTEIN:

Q. Would you tell us why it is not safe, Dr. Spaet?

A. Yes, because it precludes the use of the appropriate treatment in the patient who has a major problem. If a drug is inefficacious and it is being used instead of an efficacious agent then it is not safe.

The COURT. If it is harmless what difference is there to keep you from using both of them?

The WITNESS. But the point is if the agent——

The COURT. Oh, no. I just want you to explain [93] to me.

The WITNESS. Yes, sir.

The COURT. You said it has no affect period, it was useless; that is like a placebo—and you know what a placebo is I am sure.

The WITNESS. Yes, sir.

The COURT. Because you give me a placebo, which is nothing but sugar water, or whatever you want to call it, just to satisfy my vanity, that wouldn't interfere with giving me a pill that would do me some good, would it?

The WITNESS. May I illustrate, your Honor?

The COURT. Well, answer it, first.

The WITNESS. My answer is that it is like putting tap water in your radiator, car radiator in the middle of winter. Now, this doesn't hurt the radiator as such, but it is not safe to do it.

The COURT. If I put tap water in a radiator and I also put Zerex, I would have a pretty good radiator, wouldn't I?

The WITNESS. If you filled your radiator with tap water there would be no room for the Zerex.

The COURT. Now, that is—now you are getting at it. The question is: is this harmful, not that—and I understood you to say that it interfered with putting in, putting tap water, as you call it, in a radiator, wouldn't [94] interfere with putting Zerex unless I filled it up, would it?

The WITNESS. If tap water is offered as the efficacious way of preventing your radiator from freezing over, then an individual convinced of this would not put in the Zerex.

The COURT. Well, that is debatable.

The WITNESS. I think that——

The COURT. I understand what you are saying.

The WITNESS (continuing). There are some who wouldn't.

The COURT. You are just saying that if I took so many placebos that I couldn't hold any other pills then I wouldn't get the benefit of the other pill; isn't that what you are saying?

The WITNESS. No, your Honor, that is not quite what I am saying.

The COURT. What are you saying?

The WITNESS. What I am saying is that if a physician feels that he has an efficacious agent and gives it to a patient to stop bleeding he may use this instead of the efficacious agent.

The COURT. He may, and he would not get the bleeding stopped.

The WITNESS. He would not get the bleeding stopped and a very dangerous consequence.

The COURT. And it wouldn't be the proper [95] treatment.

The WITNESS. That is right.

The COURT. But it wouldn't show that this was a—it might show false labeling or false advertising, but it wouldn't show that this was a harmful drug, that it would cause harm.

The WITNESS. Well, can I tell you about my own experience in this respect?

The COURT. Sure.

Mr. HOFFMAN. We object, your Honor, on the ground that his experience is not relevant. It is general recognition.

The COURT. If his experience isn't relevant to forming an opinion, I don't know what is.

Mr. HOFFMAN. Your Honor, what would be would be his testimony such as he gave before on what the expert consensus is as to the safety of the product, not——

The COURT. Objection is overruled. I do not know of any better experience that a doctor or a lawyer gets than 40 years of his own practice. It is far more important to him than it is all the journals he can read.

Now, let's get on with it.

You practice law and the more you practice the more experienced you get, and you base your future on the mistakes you made in the past and hope you don't make them [96] again.

Next question.

Mr. HOFFMAN. Your Honor, could we direct the Court's attention to certain judicial decisions dealing with precisely this issue of the difference between general recognition, on the one hand, and the witness' own experience?

The COURT. We are not talking about general recognition. We are talking about this man's expertise.

Mr. HOFFMAN. These are the cases that say that is irrelevant, your Honor.

The COURT. Well, I don't think it is.

By Mr. EPSTEIN:

Q. Go ahead, Dr. Spaet.

A. Your Honor, I had a patient not too long ago who had a tonsillectomy. He had hemophilia. The tonsillectomy should not have been done. The doctor who did it gave this boy, who was bleeding for days, inefficacious agents, and when he came to me he was almost dead because the proper treatment had not been given. The reason is that this physician had been told by various sources, not appropriate ones, but by various sources that if you give A and you give B and you give C everything will be all right. Now, I think it is dangerous to tell physicians this. I think a drug that is offered as an efficacious agent in serious conditions and that does not have this effect is not a safe drug.

[97] Mr. HOFFMAN. Your Honor, we move that that testimony be stricken on the ground that there is no showing that the product that the young person in question was being given was one of the products involved in this case. We think that it is prejudicial.

The COURT. He has just said that if it wasn't properly labeled—you see you are getting excited too easy. He didn't say that your drug was improperly labeled. If you don't ask him I am—I mean about your drug—that is all I want to know.

By Mr. EPSTEIN:

Q. Dr. Spaet, is the opinion that you have just given the opinion that is shared in by your colleagues in the specialty of hematology and internal medicine?

A. I think it is.

The COURT. I want to know about this person's drug. I am still not talking about A, B, C and D. We are not trying A, B, C and D. We are determining the efficacy of this drug.

Do you understand, Doctor?

The WITNESS. I do.

The COURT. Not anybody else's. Now, let's get——

The WITNESS. I was just trying to illustrate, your Honor.

The COURT. But it has really no weight. Because [98] B and C is no good doesn't make A bad, does it? Obviously not.

The WITNESS. No. I was trying to illustrate why lack of efficacy could also mean lack of safety.

The COURT. I understand.

Mr. EPSTEIN. And my question, your Honor, was when I asked him the first question was: was it the use of plaintiff's drugs, was it the administration of the plaintiff's drugs?

The COURT. He hasn't talked about plaintiff's drugs. He is talking about A, B and C. Get him to plaintiff's drugs. Get him on plaintiff's drugs if you want to do that.

By Mr. EPSTEIN:

Q. Dr. Spaet, is it your opinion that the administration of the plaintiff's products to a patient who has just had a tonsillectomy would be a safe modality for the treatment of the bleeding condition that results from a tonsillectomy?

A. I do not believe it would.

Q. Would you tell us why not, Dr. Spaet?

A. Because if a patient is bleeding following a tonsillectomy he requires whatever the treatment is appropriate for his underlying reason for bleeding, not bioflavonoids.

Q. Is this opinion shared in by your colleagues, Dr. Spaet?

[99] A. I believe it is.

Q. Is it your opinion that the administration of the plaintiff's products to a patient who is suffering from hypertension is a safe modality for the treatment of that condition with plaintiff's products?

A. The same answer applies.

Q. Is that opinion also shared in by your colleagues, Dr. Spaet?

A. The same answer applies.

Q. Is it your opinion—well, without going through the whole length of the question, let me just say I am asking him the same question again, your Honor, and I am applying the plaintiff's products in use in a situation where there are "little strokes" as defined in the plaintiff's labeling. Would you use the plaintiff's products in that kind of a patient, your Honor,—Doctor?

A. I would not and I do not think it is a safe modality for use in it.

Q. And is this opinion shared in by your colleagues, Dr. Spaet?

A. I believe it is.

Q. Now, Dr. Spaet, how about using the plaintiff's products in connection with a diabetic retinitis?

Mr. HOFFMAN. Objection, your Honor. He is not specifying which of the products involved in this case he is [99–A] talking about. There are six, or seven or eight products, and the questions are being framed universally; the doctor is responding universally.

The COURT. I am not going to exercise any tighter control on this case than I have. If the government puts on weak evidence you take the advantage of it; if they put on strong evidence you rebut it. Now, if you—I will agree with you: his testimony is a little vague and indefinite, and I have suggested a dozen times—I mean to counsel, not the doctor, that it will have more weight with me if he talks about A, B and C instead of talking about generalities. That is up to counsel. And I agree that you have more than one drug involved here.

Mr. EPSTEIN. The problem is, your Honor——

The COURT. If his testimony is generally they are not good for any of the purposes for which the label says they are let him say so, and then he can bring out they are good—if he says that they are harmful for everything set forth on the label, you want to generalize it, let him do it.

Mr. EPSTEIN. But the generality only went because they are all bioflavonoid products that we are dealing with, and I thought that the doctor had already told us that he was using—his answer applied to the use of bioflavonoids, but I will specify with each of the products, then, your Honor, so we will have that clear.

[99–B] The COURT. I mean if there is any dispute, and again let's get this——

Mr. EPSTEIN. Yes.

The COURT (continuing). If the doctor is familiar with the labels in question here on the drugs here involved, all he's got to do is to say, "I have read that label, I am familiar with it, and in my opinion this drug will not accomplish any of those purposes," if that is his answer. I don't know what his answer is.

By Mr. EPSTEIN:

Q. Dr. Spaet, are you familiar with the labeling and the representations that are made for the plaintiff's C.V.P. capsules?

A. I am.

Q. Are you familiar with the labeling——

The COURT. Let's take those capsules and let him say what—he says he is familiar with them. Now ask him a question about them.

Mr. EPSTEIN. All right.

By Mr. EPSTEIN:

Q. Doctor, would you use——

The COURT. Not would he use.

Mr. EPSTEIN. Excuse me.

By Mr. EPSTEIN:

Q. Doctor, is it your opinion that the administration [99–C] of the plaintiff's C.V.P. capsules to a patient who is suffering or who has a condition of habitual and threatened abortion would be a safe modality for the treatment of that condition?

A. I believe it would not.

The COURT. Does the label say it would, in your opinion?

The WITNESS. The label in my opinion says that it is offered for the treatment of it.

The COURT. All right.

Mr. HOFFMAN. Objection, your Honor. He is not qualified as an expert in the meaning of the labeling. But in any event we think the court should determine that.

The COURT. I will say this much, if he is not labels are not worth the paper they are written on.

Mr. HOFFMAN. Your Honor, we think the court can determine what the labeling means, not this witness.

The COURT. I am not as expert as he is. If you use big language I don't know how I am going to know whether this pill is good for bleeding from abortions or whether it isn't if an expert doesn't tell me.

Mr. HOFFMAN. Your Honor, the question was not whether the product would be good for that condition. The question was whether that is what the labeling recommended it for.

[99–D] The COURT. Well, he says it does.

Mr. HOFFMAN. That is the determinative piece of paper.

The COURT. He says it does. Now, you point out—let him show you as an expert where it doesn't say that.

All right. Go ahead.

By Mr. EPSTEIN:

Q. Doctor, why would you not use the plaintiff's products C.V.P. capsules for a patient who is suffering from the problem of habitual and threatened abortion?

A. Because the efficacious therapy for that is other and again by using this you are relying on something——

The COURT. Doctor, so we get this, there may be better, that is not the question in this case——

The WITNESS. No, your Honor; other.

The COURT. I say there may be other methods of treating it. The question is whether or not basically this is false labeling, whether or not the drug, it will not do what it says; the mere fact that another drug—in other words, doctors might agree that aspirin and Bufferin, which are technically two different labeled products, both might be proper for a simple headache—do you follow what I mean?

The WITNESS. I do, sir.

The COURT. That is what I am referring to here, so let's confine it to this drug, tell him why it is either no [99–E] good or harmful, whichever it might be, in the treatment for bleeding following abortion.

The WITNESS. On the basis of the available literature, sir——

The COURT. All right.

The WITNESS (continuing). The evidence that it is of benefit is far from adequate; it is inadequate in my opinion.

The COURT. All right.

The WITNESS. Now, the same principles that I have been applying in other conditions, I believe, sir, apply here as well, that if you have an inefficacious product in an attempt to treat a major illness and use that instead of an available method that is efficacious, then the use of this product, the offering of it is a danger insofar as the efficacious therapy is being forestalled.

The COURT. You leave that argument to your counsel.

The WITNESS. Okay.

The COURT. I mean now we just want to get the facts. You may be on sound ground, see, but your factual evidence is that in your opinion, based on experience and based on medical literature, that this capsule just mentioned would have no therapeutic or curative effect on the ailment referred to.

The WITNESS. Yes, sir.

[99–F] The COURT. That is a fact, in your opinion, so let's limit your testimony to facts.

By Mr. EPSTEIN:

Q. Doctor, is the opinion that you have just described to us the opinion shared by your colleagues?

The COURT. He said it was.

Mr. EPSTEIN. All right.

By Mr. EPSTEIN:

Q. Now, Doctor, as to the plaintiff's C.V.P. capsules, is it your opinion that the administration of the plaintiff's C.V.P.

capsules to a patient who is suffering from postpartum bleeding would be a safe modality for the treatment of that condition in that patient?

A. The same answer applies.

Q. Would you tell us why, Dr. Spaet?

A. Well, again, the studies that are available——

The COURT. If your answer, Doctor, and I don't want to cut you off, if your answer is although it is harmless it doesn't accomplish the purpose the label says it does, just say that.

The WITNESS. The same answer applies as before, basically.

The COURT. He just says it is like tap water, it is harmless, but it won't grant any relief.

Is that correct?

[99–G] The WITNESS. Yes, sir.

The COURT. All right. We will take it from there.

By Mr. EPSTEIN:

Q. Doctor, referring to the plaintiff's C.V.P. Capsules, is it your opinion that the administration of the plaintiff's C.V.P. Capsules to a patient who may be suffering from epistaxis is a safe modality for the treatment of that condition?

A. I do not.

Q. Would you tell us why not, Dr. Spaet?

A. The same answer applies as before.

Q. Is that opinion also shared by your colleagues?

A. To the best of my knowledge.

Q. As to the C.V.P. Capsules, is it your opinion that the administration of plaintiff's C.V.P. Capsules to a patient who is suffering from diabetic retinitis would be a safe modality for the treatment of that condition?

A. I do not.

Q. Would you tell us why not, Doctor?

A. The same answer applies.

Q. What is diabetic retinitis, sir?

A. These are changes in the retina of the eye that are a consequence of the underlying diabetic condition.

Q. What kind of treatment do you administer to [99–H] a diabetic, Doctor?

The COURT. No. I do not want him to go into that.

Mr. EPSTEIN. All right.

The COURT. It isn't necessary.

Mr. EPSTEIN. Your Honor, then I will just go to each of the specific questions.

By Mr. EPSTEIN:

Q. Dr. Spaet, is this opinion that you just stated the opinion that is shared by your colleagues?

A. To the best of my knowledge.

Q. Is it your opinion that the administration of plaintiff's C.V.P. Capsules to a patient who is suffering from an ocular disorder is the safe modality for the treatment of that condition?

A. I do not.

Q. Would you tell us why not, Doctor?

A. Because the same answer applies as before. Your Honor, should I go through it separately each time?

The COURT. Not if it is the same answer.

The WITNESS. It is basically the same answer.

The COURT. And I understand your answer to be, Doctor, on each of these, and I follow your reasoning, that the label that the company puts out for this capsule would indicate to the average doctor that it was effective [99–I] in the curative of that particular ailment?

The WITNESS. Yes, sir.

The COURT. All right. Now if that applies to each one of them you can say it as to all of them to save time. But I just want to make sure that the label says to this doctor it will do that and in his opinion and in the opinion of his colleagues it is not only won't do it, it is unsafe because it keeps a doctor by this false advertising from using what otherwise he would have used.

Is that what you are saying?

The WITNESS. All right. Now, that applies to all of them; then he can find out why, what is wrong with this.

By Mr. EPSTEIN:

Q. I will ask you, then, the same question, Dr. Spaet, as it applies to a patient who has menorrhagia?

A. Yes, sir, it is the same answer.

Q. How about Rh incapatibility?

A. Same answer.

Q. And rheumatoid arthritis?

A. Same answer.

Q. And hemorrhagic duodenal ulcer?

A. Same answer.

Q. And ulcerative colitis?

A. Same answer.

Q. And hemorrhagic cystitis?

[99-J] A. Same answer.

Q. Postoperative bleeding?

A. Same answer.

Q. Radiation therapy?

A. Same answer.

Q. Now, I will ask you the same list of questions, Dr. Spaet, for the same conditions, and I will ask you is it safe to use plaintiff's product Duo-C.V.P. for the same disorders and the same line of questioning?

A. Same answer.

Q. And is this opinion also shared in by your colleagues?

A. To the best of my knowledge.

Q. I will ask you if the same is true for plaintiff's product C.V.P. with K?

A. Same answer.

Q. And you would give the same answer for each of the disorders or physical illnesses which we have gone through in this specific list on the use of their products?

A. I would.

Q. As to for the use of plaintiff's product Duo-C.V.P. with K?

A. Same answer.

Q. And to the same list of conditions which I have described from the previous line of questioning?

[99-K] A. Yes.

Q. And would those opinions be shared in by your colleagues?

A. I believe so.

Q. And as to Duo-C.V.P. or——

(Mr. Epstein conferred with his co-counsel.)

Mr. EPSTEIN. All right. Excuse me a minute. Did I understand your Honor to say that you did not want to go into what would be the therapy of choice in various of these disorders, you were not going into.

The COURT. I don't think we need that evidence.

Mr. EPSTEIN. Yes.

The COURT. If you have three choices of a remedy one doctor might use one and one might use the other. I mean that is common practice.

Mr. EPSTEIN. Yes.

The COURT. I understand his theory is that by using this method——

Mr. EPSTEIN. That is right.

The COURT—It precludes the doctor from using a proper method.

Mr. EPSTEIN. Right.

The COURT. And, therefore, it is harmful. That is what he is saying.

Mr. EPSTEIN. Right.

[99–L] The COURT. Aren't you, Doctor?

The WITNESS. Yes, sir.

By Mr. EPSTEIN:

Q. Dr. Spaet, what is capillary permeability?

A. That is the ability of the capillary to allow normal constituents of the blood to pass through it, to nourish the tissues.

Q. In your opinion is it sound medical judgment to eliminate or remove capillary permeability or decreased capillary permeability?

A. No.

Q. Would you tell us why?

A. Capillary permeability is the means whereby things are transported from the blood to the tissue and if you remove this, of course, then everything we go by is eliminated, all the traffic stops.

Q. What is capillary fragility?

A. Yes. This is the liability that the capillaries have to rupture; in other words, how easily you can rupture capillaries is a measure of their fragility.

Q. Let me ask this, then: If an individual were brought to you and you were told that he had abnormal capillary fragility, what is the medical significance of his state?

A. This means that he has a likelihood of being more susceptible to bleeding.

[99–M] Q. If he is more susceptible to bleeding, do you treat the capillaries or give a treatment for the capillaries in this individual who would be susceptible to bleeding?

A. Not as such. You treat the underlying condition that is causing it.

Q. How do you establish this underlying condition?

A. By a series of diagnostic tests that we have available to us.

Q. What are the causes of capillary fragility and capillary permeability?

A. It can be caused by scurvy. It can be caused by diabetes. It can be caused by allergies. It can be caused by a whole host of things.

The COURT. Excuse me. This is most interesting and I love a medical education. Sometimes it saves me going to a doctor and when it does I get in trouble, because I don't remember it just right. But seriously, what has this got to do with this case? And you say his label says that use my drug, my capsule and you will be cured of capillary fragility? Do you say that is what his label says?

Mr. EPSTEIN. Yes.

The COURT. Ask him if his label includes that and is it curative or harmful for it.

Mr. EPSTEIN. Well, I completely——

The COURT. That is the question.

[99–N] Mr. EPSTEIN. Yes. The labeling is already in evidence, your Honor. It has been agreed to.

The COURT. I know, but I may not be able to read it. I want an expert to tell me what it says.

Does the label on his drugs—I will ask you. He doesn't want to find out. Do these labels to a doctor——

The WITNESS. Yes.

The COURT (continuing). Clearly indicate that the use of these drugs will cure or have a curative effect on this capillary fragility that he has been describing?

The WITNESS. Irrespective of cause almost.

The COURT. What?

The WITNESS. Almost irrespective of cause.

The COURT. And the label says that?

The WITNESS. Yes.

The COURT. And you disagree with that?

Mr. HOFFMAN. Your Honor, we think the document speaks for itself.

The COURT. I will let you examine him what the label says. What?

Mr. HOFFMAN. We think the document speaks for itself.

The COURT. You can ask him to point out if you don't think it says that.

Mr. HOFFMAN. We will, your Honor.

[99–O] The COURT. All right. You can ask him what language is in the label. Get it out and show it to him, and I will look at it at the same time.

He says that, and he says it has the same effect as these other drugs, none—it is harmful.

Next question.

By Mr. EPSTEIN:

Q. Doctor, in summary to all of these specific questions that we have asked, do you—is it your opinion that it is medically safe to use the plaintiff's bioflavonoid products for altering capillary permeability and/or capillary fragility or in the treatment of any of the diseases and conditions that are prescribed, recommended or suggested in the various items of written matter, printed or graphic descriptions of the plaintiff's products?

A. It is my opinion that across the board these are neither efficacious nor safe.

Q. Was this your opinion, did you hold this opinion also, Dr. Spaet, on October 9, 1962?

A. I did.

Q. And do you hold that opinion today?

A. I do.

Q. Is that opinion concurred in by your colleagues also?

A. As far as I know.

[99–P] Q. And can you tell us whether your colleagues also concurred in that opinion on October 9, 1962?

A. To the best of my knowledge.

Mr. EPSTEIN. I have no further questions on direct, your Honor.

The COURT. All right. You may cross-examine him, and he is an expert, so I will allow you to bring out anything that you disagree with, but I will ask him one question first.

Doctor, from some of the exhibits, and I don't remember the figures, but speaking in quantities apparently they are distributed and sold quite a bit, a large quantities of this medication.

The WITNESS. Yes, sir, your Honor.

The COURT. Are you familiar with the relative amounts that they have alleged to have sold?

The WITNESS. I understand that the sales are something like $5 million a year, or something like that.

The COURT. My question is what explanation, if any, do you have to offer why practicing doctors throughout the country

would continue to use these drugs for these purposes if the results therefrom turned out to be in their patients what you have just indicated is the result? Why do doctors keep on using pills for eight years when experience should teach them if that is the result that it has absolutely [99–Q] no effect on the patient?

The WITNESS. Your Honor, would you like me to speculate?

The COURT. No. I want you to speak as a doctor if you can answer the question. I don't want any speculation. If you know.

The WITNESS. I don't know the answer to it, but I know that it is a wide-spread phenomenon that is well known throughout history.

Mr. HOFFMAN. I object to this line, your Honor. It is speculation.

The COURT. You may object. I want to get information.

Elaborate a little.

The WITNESS. Well, we know that inefficacious views as to explanations for things or how to achieve things have been held as long as man has records. The efficacy of magic, for example, was held by societies from time immemorial—why they were convinced that it worked.

The COURT. But it ceases to exist after a time, doesn't it?

The WITNESS. Well, eons.

The COURT. We have—most of us have quit witchcraft.

The WITNESS. But look how long it took us, your [99–R] Honor.

The COURT. I mean—well, no—I just asked you. Give the answer eight years isn't long enough to satisfy the average doctor. Is that what you mean?

The WITNESS. What I mean is that I can give what I consider——

The COURT. No. I mean I want to get your reasoning. As to witchcraft, it is time you are saying; magic is time.

The WITNESS. Yes.

The COURT. Of course a lot of things doctors do today they didn't do 10 years ago.

The WITNESS. That is right, sir.

The COURT. It is continually changing in the practice.

The WITNESS. I will tell you——

The COURT. How long does it take a doctor, the average good doctor, to find out, based on his own experience, that a pill advertised to stop bleeding, and that is what this is reduced to simplicity, or curtail bleeding, isn't that right?

The WITNESS. That is right, sir.

The COURT. How long does it take a doctor with bleeding patients to find out the pill doesn't produce the desired result—eight years, two years, five years, thirty years?

[99–S] The WITNESS. I think that with some doctors it takes replacement of that doctor.

The COURT. In other words, you say that the doctor then is in your opinion gullible from the pharmaceutical house and will accept anything they say?

The WITNESS. Also I think that that doctor may have had a good experience in which he gave such a medication to a patient early in the game, the patient stopped bleeding perhaps for reasons that had completely nothing to do with the agent, and he said, "Ah," and then everytime something like this comes along he tries it again.

The COURT. That would not be the situation in $5 million worth, would it?

Mr. HOFFMAN. Your Honor, I object to this as speculation and not tied to the——

The COURT. I understand, but I want to do a little speculation.

The WITNESS. It is admittedly so.

Mr. HOFFMAN. Note a continuing objection.

The COURT. I mean I—seriously I want to find out. This is favorable to you and you want to cut it off. I really want to know why doctors do this because the evidence shows they do it, and then I want to know why the Government doesn't send out labels "Don't use these pills," or why they don't take them off and why it takes the government eight years. [99–T] There are a lot of things I want to know.

The WITNESS. Your Honor——

The COURT. Why it takes them eight years to stop something that you knew in 1962, when you served with the committee in '68, and they haven't issued any orders to cease and desist, as far as I know. These are questions they are getting to get answer for me.

All right.

The WITNESS. Your Honor, I have been involved in the whole process of how to get up-to-date medicine in the hands of people who are not associated with a teaching institution. At the New York Academy of Medicine this was one of our major problems.

We found that no matter what you do there is a group of physicians whom you cannot reach. You cannot reach them by television, you cannot reach them by any of the means that we normally——

The COURT. Do I understand that these pills are only being used by that class of doctor?

The WITNESS. I think so, sir.

The COURT. They are not being used generally by doctors in the field according to your experience?

The WITNESS. I do not know—

The COURT. They are not being used generally by reputable doctors?

The WITNESS. I do not know that they are on [99–U] the pharmacy list.

The COURT. Do you know anybody who uses them?

The WITNESS. No, sir.

The COURT. Do you know anybody that has ever used them?

The WITNESS. No, sir.

The COURT. Have you ever talked to a doctor, you or the committee, that has ever used them to determine what the results were?

The WITNESS. To the individual physicians, no, sir.

The COURT. Did you ever send a questionnaire out as a committee or anything to the doctors that were known to be using these pills for the purpose of getting their experiences?

* * * * *

[100] (AFTER RECESS)

[Whereupon, Theodore Spaet, the witness on the stand at the time of recess, resumed the stand, was examined and testified further as follows:]

The COURT. So that I will be fully informed, and maybe the counsel can stipulate this, are these drugs—I am talking about the ones in issue here—are they dispensed, in the main, through doctors, or are they dispensed, in the main, to the public absent doctors, which are they, or both?

Mr. HOFFMAN. Your Honor, the products are available, with labeling that simply says it is a dietary supplement, and it says nothing more than that, over the counter. The only information suggesting that the products are useable in abnormal capillary fragility and permeability, specifically, the only label-

ing involved in this case is labeling that is available to physicians. As to that use, it is a prescription product and we are not concerned with any use of the product that is in this case that is not a prescription product. I believe the government will stipulate that.

The COURT. That is what I was getting at. These are prescription; in other words, they are dispensed through doctors?

Mr. EPSTEIN. Yes, sir.

[101] The COURT. All right. I just wanted to make sure.

Mr. EPSTEIN. We will stipulate they are dispensed through physician prescriptions, Your Honor.

The COURT. That is right. All right. And it is an alleged mislabeling, as far as the doctor is concerned, and not a new drug, as far as they are concerned. I understand.

All right.

CROSS EXAMINATION

By Mr. HOFFMAN:

Q. Good afternoon, Dr. Spaet. Dr. Spaet, I believe you testified on direct examination that you had not heard of the C.V.P. products, that is, the products involved in this case, until about 1966; is that correct?

A. Yes, sir.

Q. I believe you also testified——

The COURT. Wait a minute. I did not understand that. He said he knew of this situation in 1962.

Mr. HOFFMAN. Your Honor, I was just getting to that.

The COURT. That is what he said.

Now, you gave your opinion that these had that effect in 1962; is that correct?

The WITNESS. I was not made familiar, Your Honor, [102] the bioflavonoids of this company until 1966, when I sat on the Drug Efficacy Committee.

The COURT. All right. Then his knowledge of it will be limited to 1966. He said he was not familiar with it.

Mr. EPSTEIN. Your Honor, let me just try and straighten one important issue out on that subject. The thing that the doctor testified was as to what bioflavonoids are. The government and counsel for the plaintiffs have already stipulated what these products contain. That is already in evidence.

The COURT. We understand that.

Mr. EPSTEIN. Because my important consideration here is that Dr. Spaet, as an expert in this area, did know about bioflavonoids, and bioflavonoids fall in the same group so that, just because he may not have specifically been aware of these products that we talked about until 1966, does not mean he did not have expertise to talk about the safety and efficacy of bioflavonoids on October 9, 1962.

The COURT. We will agree that he had expertise as to the general subject in 1962, but, by his own admission, he never even heard of these drugs in 1962, so he could not have any knowledge of them in 1962.

The WITNESS. Yes, sir.

The COURT. Is that right?

The WITNESS. Yes, sir.

[103] The COURT. But he did have actual knowledge of these drugs at the beginning of 1966.

The WITNESS. Yes, sir.

The COURT. All right. Now, let's take it from there.

By Mr. HOFFMAN:

Q. Dr. Spaet, you said that you discussed bioflavonoids generally around 1962 with other experts?

A. Yes, sir.

Q. And you testified that there were possibly as many as ten, is that correct?

A. Experts, yes.

Q. Experts?

A. Yes.

Q. Can you name ten?

A. Can I name ten experts?

Q. With whom you discussed the safety or efficacy of bioflavonoids generally around 1962?

A. No, I could not name the actual individuals with whom I discussed it. That is an estimate.

Q. Can you name one?

A. One person with whom I discussed it?

Q. One expert of those ten.

The COURT. One doctor in your field.

The WITNESS. Not under oath, certainly not.

[104] By Mr. HOFFMAN:

Q. Could you specify under oath where such—one such conversation took place, in fact, not your speculation, but where it took place and in what circumstances?

A. I would not do that unless I saw fit to record it, because I have no way of referring back to any kind of accurate statement as to such conversation.

Q. So, then, there is no evidence that any such conversation actually took place, is that correct?

The COURT. No, that is not correct. We have his evidence that it took place, so there is some.

By Mr. HOFFMAN:

Q. But you cannot tell us where it took place or exactly when or with whom?

The COURT. He has agreed that he cannot name the people or the time or the place, but he still says he had the conversation, so there is some evidence.

Mr. HOFFMAN. Your Honor, we would move to strike that evidence.

The COURT. Motion is denied. It goes to the weight of it.

By Mr. HOFFMAN:

Q. Doctor, you have testified that you are a hematologist; is that correct?

A. Yes.

[105] Q. And, I believe, you also testified that the subject of hematology deals with blood disorders; is that correct?

A. Yes, but not only——

Q. Are hematolotists usually or commonly concerned with blood vessel abnormalities?

A. Some are.

Q. Are you?

A. I am.

Q. Doctor, I believe you have the labeling for these products in front of you?

A. I do.

The COURT. Let me have a copy of it so we both can read.

Mr. HOFFMAN. This is attached to the request for admissions.

The COURT. All right, whatever exhibit it is in—Government's request for admissions?

Mr. HOFFMAN. No, the defendant's, Your Honor—I am sorry—the plaintiff's.

The COURT. All right. Request for admissions, all right. Which one are you referring to?

Mr. HOFFMAN. The one with Exhibits A through K.

The COURT. All right, I have it here.

By Mr. HOFFMAN:

Q. Dr. Spaet, I direct your attention to Exhibit A, [106] which——

The COURT. That is the one that has a picture on it?

Mr. HOFFMAN. That is the one that has pictures of what looks like parts of a box.

The COURT. C, B, T, and so forth?

Mr. HOFFMAN. That is right.

The COURT. All right.

By Mr. HOFFMAN:

Q. Dr. Spaet, would you please direct the Court's attention and mind to the place on Exhibit A, where the product is recommended for any one of the underlying conditions for which, you testified, you thought the product was unsafe because ineffective.

A. That is——

Mr. EPSTEIN. I am raising an objection, Your Honor, to that question on the grounds that the documents to which we referred and the answers to which Dr. Spaet responded were to all of the statements in it, and we did not specifically come to any one exhibit to ask for his answer. The statements are contained in more than one.

The COURT. Objection is overruled.

I asked the Doctor myself, and I understood him to say so, if the labeling that the company put out for the information of the doctor, in his opinion, would indicate to [107] the doctor that this capsule would do something for a specific ailment, and you went through several of them, and he said that the label so stated. Now, I think he is entitled to make him point out in the label where it refers to stopping bleeding from abortions. That is one of your questions.

Mr. EPSTEIN. I have no objection if he asks the question that way, but that is not what he did, Your Honor.

The COURT. What did he do?

Mr. EPSTEIN. He asked him if——

Mr. HOFFMAN. This is cross, Mr. Epstein.

The COURT. Objection is overruled.

Go ahead. I think it is a fair question.

The WITNESS. Your Honor, may I have some clarification——

The COURT. Sure.

The WITNESS (continuing). As to what constitutes a label? Is a label merely what is stuck on the bottle? Is a label——

Mr. HOFFMAN. We are talking about Exhibit A.

The COURT. It is in Exhibit A. That is what is given to the doctor.

The WITNESS (continuing). Because there are other material——

The COURT. Everything in Exhibit A is what he says was given to the doctor.

Mr. HOFFMAN. We are not saying that was all, [108] Your Honor, but I started with Exhibit A, and I would like Dr. Spaet to testify.

The COURT. That is the label, isn't it?

All right. Now, ask him the question. You want to know about Exhibit A. What do you want to know?

By Mr. HOFFMAN:

Q. I would like to know, Doctor, where in Exhibit A the product Duo-C.V.P. with Vitamin K, or any of the other labels that are reproduced on that sheet——

A. It is not to be found on that sheet.

Q. Not to be found on that sheet?

A. That is right.

Q. Now, would you kindly point out on Exhibit B where it is recommended that the product be used to cure the underlying condition which produces, or, in conjunction with which may be found abnormal capillary fragility and permeability.

A. It is not offered to cure the underlying condition. It is offered to cure the manifestation.

Mr. HOFFMAN. Thank you.

The COURT. On what page is it offered to do that? Whereabouts?

The WITNESS. This is on Exhibit B, on the line that says "Indications".

Mr. HOFFMAN. We will accept that answer, Your [109] Honor.

The COURT. All right.

Now, let me see it, though. That is on B—Is that the first page of B or——

Mr. HOFFMAN. Yes, I believe it is, Your Honor.

The COURT. The one, at the top it is marked "1962–63", and so forth?

Mr. HOFFMAN. Yes.

The COURT. Where is this line that you are re-referring to, Doctor?

Mr. HOFFMAN. Your Honor, I think he is referring to the whole card, which is a single document and includes different columns, and so forth, and we are very satisfied with that answer and would like to move forward.

The COURT. You may be satisfied with it, but I want to see it.

Where is it?

Mr. EPSTEIN. Sorry, Your Honor, this is the wrong document.

The COURT. I've got the wrong document. No wonder I cannot find it. Give me the right document. This is request for admissions.

Mr. EPSTEIN. That is ours, Your Honor.

The COURT. You do not want that one?

Mr. EPSTEIN. No, we have the other one.

[110] Mr. HOFFMAN. Here is another set of the tabs.

The COURT. All right. We've got so many of them here. Here it is. This is the one, I assume. Is this it?

Mr. EPSTEIN. That is exactly it, Your Honor.

The COURT. All right. Now we are back to B.

Mr. EPSTEIN. Excuse me.

The COURT. All right.

Now, you say it is the first line. Where, Doctor, that you just said it indicates——

The WITNESS. Indication, the whole area that is covered by indications.

The COURT. Where is that?

The WITNESS. It is on the right hand side of the card.

The COURT. Oh, "Indications, Dosage, Adult".

The WITNESS. Are we looking at the same sheet?

The COURT. I hope we are.

The WITNESS. It says "Exhibit B."

Mr. EPSTEIN. Your Honor, it is on the page behind the tab that says "B" on it. It is the page directly following the——

The COURT. The second page, where it says "Indications of Dosage continued"?

The WITNESS. The second page?

Mr. HOFFMAN. What is the second page?

[111] The WITNESS. There is no second page.

Mr. HOFFMAN. Right here.

The COURT. I've got Exhibit B. There is page 1, Exhibit B, page 2.

The WITNESS. Okay.

The COURT. Have you got that?

Mr. HOFFMAN. I believe so, Your Honor. Each page appears to be a picture of a card similar to the one——

The COURT. That is right.

Mr. HOFFMAN (continuing). Setting on the clerk's desk.

The COURT. And it says, "Capillary fragility, Duo-C.V.P." Now, I don't see—On page 2, it doesn't say anything about indications and dosage. It does——

The WITNESS. On page 1, it does.

The COURT. Yes.

Mr. HOFFMAN. Are we looking at the same——

The COURT. Yes. Have we got the same?

Mr. HOFFMAN. Yes, we are, Your Honor.

The COURT. All right.

What line on that page do you want me to read?

Mr. HOFFMAN. Your Honor, in the right hand column, which begins "C.V.P. and Duo-C.V.P." parallel——

The COURT. Yes.

Mr. HOFFMAN. Okay. The first indented subparagraph.

[112] The COURT. All right.

Mr. HOFFMAN. Help to maintain normal capillary permeability, and it goes on——

The COURT. All right.

Mr. HOFFMAN. Now, I believe Dr. Spaet has testified that, in his opinion, this labelling represents the products involved, not for the underlying condition in conjunction with which abnormal capillary permeability and fragility are found, but, rather, for what the Doctor termed the manifestation. Perhaps the symptom would be a layman's word.

The COURT. All right.

By Mr. HOFFMAN:

Q. Is that correct, Doctor?

A. This is the way it is stated.

The COURT. All right.

By Mr. HOFFMAN:

Q. Doctor, can you think of any reason why a physician should not attempt, if, in his judgment, he so chooses, to treat both the underlying condition and what we have called the manifestation?

A. Well, I think that a physician should certainly try to do the combination of the two. However, when a drug is offered to treat a symptom and the symptom itself is what the physician sees, that may be all he does, if this is how he is indoctrinated.

[113] Q. That may be all he does, you say?

A. Yes.

Q. Is that all he does?

A. Frequently it is.

Q. In your judgment, is such a physician a competent physician?

The COURT. Objection——

The WITNESS. In this particular activity, no.

The COURT. Objection sustained. I am not going to let him pass on the competency of any other doctor.

By Mr. HOFFMAN:

Q. Dr. Spaet, can you direct the Court's attention and mine to any place in Exhibit B or, indeed, anywhere else in this set of ten exhibits, in which it is stated or suggested by implication that these products are the exclusive therapy to be used in any particular patient's case?

A. I think I can.

Q. Please do.

A. All right. It says the anti-hemorrhagic effect——

The COURT. What page are you reading on, Doctor?

The WITNESS. I am reading on page 2 of Exhibit C.

The COURT. Exhibit C, page 2. All right.

The WITNESS. That is right.

The COURT. All right.

[114] The WITNESS. It is the paragraph entitled, The Physiologic Effects of C.V.P. That is the entire section.

The COURT. All right, I see it, the left hand column. All right.

The WITNESS. Right.

It says: "Clinically, the anti-hemorrhagic effect of C.V.P. has been demonstrated in such bleeding conditions——" And there is a list, but I would like to emphasize the last term on the list. It says, "Hemorrhagic diatheses". Now, when this is

offered as a treatment of hemorrhagic diatheses, what the company is saying, in effect, is that anybody who bleeds from any reason should be treated with this agent, and no indication is given that there should be any other form of treatment. This is a treatment for hemorrhagic diatheses that is being offered. That includes hemophilia; it includes patients who have——

Mr. HOFFMAN. Excuse me, Dr. Spaet.

The WITNESS. This is the common understanding——

The COURT. Now, let him answer.

Mr. HOFFMAN. I would like to have that answer stricken as not responsive to the question.

The COURT. Let him answer.

The WITNESS. This is the common understanding as to what the physician means by hemorrhagic diatheses,——

The COURT. All right.

[115] The WITNESS (continuing). And I would like to make it perfectly clear that when the term "hemorrhagic diatheses" is used, this is a blanket covering any abnormal bleeding condition.

The COURT. That is what you understand the word to mean and what doctors understand it to mean?

The WITNESS. That is right.

Mr. HOFFMAN. But that was not the question, Dr. Spaet, and I move to strike the answer as not responsive.

The WITNESS. The question is, this is being offered to treat hemorrhagic diatheses and anything that is left out in any previous statement of what it is offered to treat is included in the term "hemorrhagic diatheses".

By Mr. HOFFMAN:

Q. Dr. Spaet, the question was: where, in that paragraph does it say, expressly or by implication, that C.V.P. is to be used or should be used as the exclusive therapy for hemorrhagic diatheses or any of the other underlying conditions that are listed in the preceding lines?

The COURT. He said that is what it means to him right there.

By Mr. HOFFMAN:

Q. Is that the way you interpret it, Dr. Spaet?

The COURT. That is what he said.

The WITNESS. That is the way I interpret the [116] company to mean it.

By Mr. HOFFMAN:

Q. No. The question is——

A. If the company offered penicillin, it would not say——

Q. Excuse me, Doctor.

A. (continuing). The giving of the penicillin would give oxygen.

Q. Doctor, wait a minute. You are not answering my question.

A. I understand——

Q. I respectfully ask you to wait until a question is asked.

The COURT. He has answered it. Go ahead. Next question. You may not agree with his answer, but that is what he says it does. To him, it means that.

By Mr. HOFFMAN:

Q. Dr. Spaet, I believe your answer was that this is what you thought the company meant. The question was: Is that what you understood it to mean?

A. That is what I understood it to mean, yes.

Q. So, in effect, you would be taken in by this?

Mr. EPSTEIN. Your Honor, I object to the form of the question.

The COURT. Objection is overruled.

[117] Let's get on with this case. The Doctor will take care of himself.

The WITNESS. Shall I answer the question as to whether I would be taken in?

The COURT. If you want to.

By Mr. HOFFMAN:

Q. I think I would like to have an answer, yes.

A. No, I wouldn't.

The COURT. He would not believe it is what he is going to tell you. Next question. Even though it said it—Isn't that right, Doctor?

The WITNESS. That is right.

The COURT. But he says others would.

Now, let's get on with the case.

By Mr. HOFFMAN:

Q. Would other doctors believe it?

A. Pardon me?

Q. Would other doctors believe it?

A. Absolutely. They do.

Q. On what do you base that statement?

A. On the fact that they publish papers on it.

Q. So you disagree with those papers?

A. Yes, absolutely.

The COURT. Now, wait a minute. You say other doctors published papers that these bioflavonoids did do what [118] this company says it does?

The WITNESS. That it stops bleeding.

The COURT. I say, other doctors published papers to that effect?

The WITNESS. That is right.

The COURT. Well, that is the other doctors' opinion, then, isn't it?

The WITNESS. That is right.

The COURT. He is entitled to his opinion, the same as you are entitled to yours.

The WITNESS. Quite so. I am just pointing out that he did, indeed, believe it.

The COURT. That would not follow that he was taken in. The other doctor might be right and he might be wrong.

Now, I understand that some doctors do agree that it does the very thing that you say it will not do.

The WITNESS. That is right, they do.

The COURT. So we now have it in the record. It is not a consensus.

Mr. HOFFMAN. We have in the record, not only from Dr. Spaet, but a stipulation from the plaintiff, that there is not a consensus in favor of the products' effectiveness.

* * * * *

[130] * * *

By Mr. HOFFMAN:

Q. Dr. Spaet, are you familiar with the specific component ingredients of the plaintiff's C.V.P. bioflavonoid products?

A. Do you mean biochemically?

Q. Yes.

A. No, I am not.

Q. They are in evidence in this case. Is it your understanding that the plaintiff's bioflavonoid products contain the identical

constituents with the other bioflavonoid products which were reviewed by your panel?

[131] A. It is my understanding that there is variation from one corporation to another.

Q. I would direct—Let me ask you a question, Dr. Spaet: Is it valid to equate all bioflavonoids with respect to efficacy for all conditions of use that are represented on the label? What would your answer be to that question?

A. My answer would be that until efficacy is demonstrated for any material, there is no efficacy for it.

Mr. HOFFMAN. I do not believe that is a responsive answer, Your Honor. I would move to have it stricken.

The COURT. Just ask him the next question. There is no use to strike it. It is in there.

By Mr. HOFFMAN:

Q. I would like to ask for an answer to this question: Is it valid to equate all bioflavonoids with respect to efficacy?

The COURT. In other words, do they all use—do you——

Mr. HOFFMAN. Are they all alike?

The COURT. Do you equate them all the same?

The WITNESS. I have no idea whether it is valid or not to equate them or not at this point.

The COURT. All right.

The WITNESS. I do not think the evidence is in that indicates whether such a statement can be answered.

[132] Mr. HOFFMAN. Your Honor——

The COURT. The answer is, if they do have different constituents, they are not necessarily going to have the same end results; isn't that correct?

The WITNESS. That is quite possible, but that doesn't mean that just because one is different from another, it is going to develop a sudden miraculous efficacy.

The COURT. No, and it does not mean that it won't, either, does it?

The WITNESS. No, it doesn't.

The COURT. What?

The WITNESS. That is true.

The COURT. So, therefore, you cannot answer it. Without knowing the constituents, you cannot give an answer.

The WITNESS. I thought that is what I said.

The COURT. That is all you've got to say. These questions are not hard to answer.

Mr. HOFFMAN. Your Honor, I would like to direct the witness's attention to pages 51 and 52.

The COURT. He has answered. He says, without knowing the specific contents, he does not know what the end result will be.

Mr. HOFFMAN. Your Honor, this is in the nature of impeaching that answer in that he testified on deposition, when asked that precise question, "Is it valid to equate all [133] bioflavonoids with respect to efficacy for all conditions of use that are represented in the labelling?

"A. Probably not.

"Q. Would you explain that?"

The COURT. That is the same answer he made now, only——

Mr. HOFFMAN. Page 52.

The COURT. He said definitely not, now; he said there, "Probably not." That is not impeaching.

Mr. HOFFMAN. If that is the same answer, fine. I understood him to say he could not answer.

The COURT. Why isn't it the same answer? He says "definitely not" and "probably not".

Next question.

Mr. HOFFMAN. Okay.

The COURT. It just goes to the degree of it.

Mr. HOFFMAN. Would you indulge me a moment, please, sir?

The COURT. Yes, sir.

By Mr. HOFFMAN:

Q. Dr. Spaet, do you know of any reports in scientific literature, or any reports of physicians reporting on their patients' reactions, that show or suggest that any of the plaintiff's products involved in this case are toxic, per se, that is, do they affirmatively, in themselves, cause harm?

[134] A. I am unaware of any reports in the literature. I would like to say, however——

Mr. EPSTEIN. Objection.

The COURT. Objection is overruled.

What is your objection?

Mr. EPSTEIN. My objection is that that is what we did stipulate to this morning, that they were not pharmacologically toxic——

The COURT. You said they were not——

Mr. EPSTEIN (continuing). So, apparently, the confusion in counsel's mind as to what the stipulation was.

* * * * *

By Mr. Hoffman:

[137] Q. Dr. Spaet, are you familiar with the term "drug of choice"?

A. I am.

Q. Could you tell us what it means?

A. It means the drug that is most efficacious in treating a specific condition.

Q. Is it your view, Dr. Spaet, that any drug, other than the drug of choice, as you defined it, is an unsafe drug?

The COURT. Do we get any place with that?

Mr. HOFFMAN. I think we do, Your Honor.

The COURT. All right, answer it, Doctor.

Mr. HOFFMAN. We would like to have it in.

The WITNESS. I think it is a relative matter. The farther you get from the drug of choice, the less safe is the drug that you are using. It is sometimes—Well, you keep climbing until you reach a threshold, and then, finally, you are over it and you say, blank, it is unsafe, but it is less safe to use the drug that is not the drug of choice than it is to use the drug of choice.

The COURT. To really clarify this matter and to really muddy the waters, there are doctors who think aspirin is unsafe, don't they?

The WITNESS. I am one of them.

The COURT. All right. There are millions of doctors who think they are safe, and it is probably the most [138] commonly used drug for the most widely known number of ailments in existence, isn't it?

The WITNESS. Yes, sir.

The COURT. So, therefore, because good competent doctors like you, and I am serious by putting you in it, thinks it is unsafe, doesn't make it unsafe at all, does it? A perfect example—I am a living example of 68 years, and I've probably had thousands of aspirin.

The WITNESS. But Russian roulette, by the same token——

The COURT. I know.

The WITNESS (continuing). Can also be safe.

The COURT. I would hardly, Doctor—you are now reducing your opinion to almost a ridiculous state to put an aspirin, use of aspirin, in a class with Russian roulette. You do not mean that.

The WITNESS. I mean it just has more chambers.

The COURT. Do you mean it is equally as dangerous as playing Russian roulette?

The WITNESS. No——

The COURT. Well, I would hardly think it would be.

The WITNESS (continuing). But I have known people who have died from bleeding as a result of aspirin.

The COURT. For every one that you have known who [139] died from bleeding, other doctors can name ten thousand that have been relieved of an awful lot of pain, couldn't you?

The WITNESS. Oh, yes.

The COURT. What?

The WITNESS. I use it myself.

The COURT. I thought you did.

I mean I understand the situation, but just, per se, say something is unsafe because one man does not make it that way—I know one thing that is unsafe, and that is certain poisons you take, it is conclusive, isn't it?

The WITNESS. Oh, yes.

The COURT. You just do not make it if you drink it. That is what I call strictly unsafe.

Go ahead.

All right, go ahead.

By Mr. HOFFMAN:

Q. Dr. Spaet, what is the drug of choice, in your expert opinion, for abnormal capillary fragility and permeability?

A. It depends on what the underlying conditions is that is causing it.

The COURT. Again, we are getting back. The doctor wants to get away, and I am happy to hear him, but his drug of choice certainly would not be aspirin, but he would never convince me that aspirin was, per se, unsafe.

[140] Mr. HOFFMAN. No, I am trying to get back to this particular product, Your Honor.

The COURT. All right, let's get to the issue.

By Mr. HOFFMAN:

Q. Not for the underlying condition, what is the drug of choice, in your opinion, for abnormal capillary fragility and permeability?

A. I would like to point out that abnormal fragility and permeability is a completely different proposition. The term is misused. Let's say fragility, where they rupture more easily, that the drug of choice depends on why the patient has it. If the patient has scurvy, the drug of choice is vitamin C; if the patient has a condition in which he does not have any blood platelet, it is called thrombocytepeniaperia—if you are going to give a drug, if you are not going to take out his spleen, then you will give him prednis or one of the steriods. But the point is that there is no over-all answer that answers this question as to the drug of choice for any one of them. You have to find out why the patient has it and treat him appropriately.

Q. With all respect, Doctor, I am not asking for the drug of choice for the underlying condition or the root cause of that condition, but for the condition itself of abnormal capillary permeability and fragility. Is there a drug of choice, in your expert opinion?

[141] A. I think that it is a non-question.

Q. Well, I submit, it is a question.

The COURT. He has answered it. Go ahead. He says it depends.

Mr. HOFFMAN. Your Honor, I think the answer is non-responsive.

The COURT. All he is saying, Mr. Hoffman, is that you have to tell me what causes the condition and I will try to prescribe a drug that will relieve that condition, but if the cause is from five conditions, it may take five different drugs.

Isn't that what you are saying, Doctor?

The WITNESS. Or one of five.

The COURT. You know, I would make a good witness for you.

The WITNESS. Absolutely, sir.

The COURT. I mean, I think these questions are so obvious that I do not know why you people ask them.

Mr. HOFFMAN. I have no further questions of this witness.

The COURT. Let me just—and then to clarify the doctor—he wants to get away—Doctor, I understand, basically, your ex-

pertise and your opinion, based upon your honest findings and the opinions of your colleagues, is that this type of a drug, these bioflavonoids, as they are called, [142] are, for all practical purposes, like tap water, they are harmless, per se, and by being harmless, I mean, they do not do any good or any harm if you take them.

The WITNESS. Probably, sir.

The COURT. Since they leave the impression in the doctor's mind that they accomplish this specific result, they become unsafe because they deprive the doctor of the knowledge of having available a drug that will do that.

The WITNESS. Yes, sir.

The COURT. I mean, that summarizes it, isn't that correct?

The WITNESS. That is an accurate statement of my position, Your Honor.

The COURT. All right.

Now, I understand his position, and I will let you people argue it from there.

Do you want any further questions?

Mr. EPSTEIN. Excuse me just one moment, Your Honor, if I may.

The COURT. Certainly.

Mr. EPSTEIN. I have just a couple questions.

REDIRECT EXAMINATION

By Mr. EPSTEIN:

Q. Dr. Spaet, when you were taking about Exhibit C, if you have it there in front of you, you refer to it, I [143] will ask you to direct your attention, if you would, to Exhibit C and tell me if, beyond the paragraph which you were talking about on cross examination, are there any other representations in Exhibit C that talk about specific bleeding states or serious conditions for which this product is recommended. Just take your time and look through Exhibit C, if you would, sir.

A. Yes, there is a whole list of them.

Q. Would you tell me where they are and what they are, sir?

A. Yes. They begin on page 4——

The COURT. Page 4?

The WITNESS. That is right.

The COURT. All right, I've got 4.

The WITNESS (continuing). And it starts with habitual and threatened abortion; postpartum bleeding. It continues, epis-

taxis, otolaryngology, and tonsillectomy. It continues, purpura, ecchymosis; it continues, hypertension, and so on; it goes on and on.

By Mr. EPSTEIN:

Q. Doctor, as I understood you to describe it on cross examination, is it your opinion that when the drug is recommended in this literature for the conditions to which you have just indicated, that is the drug that is being recommended for those conditions?

[144] A. Yes. This is what I intended by labeling. Your Honor, the available literature that the physician has to him I consider essentially, basically, part of the label.

Q. Now, Dr. Spaet, on cross examination——

The COURT. Now, you would read this one, first two statements on there, if I were reading them, the first statement just says, "Three out of four habitual aborters delivered healthy babies." That could be a fact. I would not deny it, but that would not have anything to do with this pill, would it?

The WITNESS. No. That is the whole point.

The COURT. That is surplusage.

The WITNESS. Yes.

The COURT. Now, the second thing—So that would not fool any doctor to say three out of four habitual aborters deliver healthy babies?

The WITNESS. Would that it were so.

The COURT. I know, but that is what it says, "Two out of every three threatened aborters were enabled, —" Now, this is positive—"on C.V.P. treatment, to complete gestation and deliver live, healthy babies."

Well, it might be inferred that they would not have delivered healthy babies if they did not take C.V.P., but I do not think that would fool him that that helps you deliver healthy babies, would it?

[145] The WITNESS. Well, the implication is that if you are threatening abortion——

The COURT. What it comes down to is the last statement, where they say their findings show that there was a decrease in postpartum bleeding in the series of treated patients, as compared with non-treated patients.

Now, to me, that would read clearly that it, at least, had something to do with slowing down or curtailing postpartum bleedings, wouldn't it?

The WITNESS. That is the claim.

The COURT. That is the claim, and you say it has no effect on that?

The WITNESS. That is right, sir.

The COURT. All right.

I just wanted to get the statement. The first two, I think, is surplusage in there. Certainly, these pills have nothing to do with delivering babies.

The WITNESS. But, Your Honor, if you were an obstetrician, wouldn't you interpret this as a treatment, per se, for threatened and repeated abortions?

The COURT. No. If I were a very good doctor, I think I would read that if I had a bleeding patient, it might slow it down some, but I would not think it would cause me, the next time my patient got pregnant, she would or would not have a baby. I mean that is all it says there. But I would [146] certainly have to read it, that it would curtail bleeding.

The WITNESS. Yes.

The COURT. All right.

Go ahead.

By Mr. EPSTEIN:

Q. Well, Dr. Spaet, in talking about the papers, literature, that you have reviewed, are any of the other papers that you have reviewed demonstrate the proof of efficacy of these dioflavonoid products?

A. No, they have not.

Q. Have you read anything in the literature that proves the efficacy of the plaintiff's bioflavonoid products?

A. No, I haven't.

Q. In the course of your teaching duties, are you familiar with the current textbooks that are in use in the medical schools on the subject of hematology?

A. Yes. It is our policy, the policy of our department, to get all the latest textbooks, standard or unstandard, so that we have a complete collection of them.

Q. Do any of the now current textbooks that are being used in the medical schools, and most particularly on the subject of hematology, mention the bioflavonoids generally or these plaintiff's bioflavonoid products specifically as efficacious therapy in the bleeding states that we have discussed this morning?

[147] A. They do not.

The COURT. Do any of these medical journals or teachings say that they are harmful, the use of them?

The WITNESS. If I am not mistaken, Your Honor, the term does not appear in them.

The COURT. It means that they ignore it?

The WITNESS. Yes.

The COURT. They do not even mention it either way?

The WITNESS. That is right, sir.

The COURT. That leaves a big void. But they definitely, none of them, go to the trouble of saying—that warn the doctor in your field, stay away from these bioflavonoids because they cause a harmful effect?

The WITNESS. No, Your Honor, but on the other hand——

The COURT. If the doctors thought they did, why wouldn't they say so in their journal——

The WITNESS. Well, because——

The COURT (continuing). Even though this pharmaceutical house is working a fraud on the doctor, why don't the medical societies speak up like big people and say, "Our experience has convinced us that they are harmful; stay away from them"?

The WITNESS. Well, I think that the standard textbook has a different mission, and the standard textbook [148] tells the young man or the physician who is not familiar with the field what is new and what is good in it, and it does not have to go about——

The COURT. It does not warn him of the bad?

The WITNESS. There are so many bad possible things that you could fill the book with it.

The COURT. All right. I understand. You just say it only teaches modern medicine and overlooks what not to do.

The WITNESS. That is right, yes, sir.

By Mr. EPSTEIN:

Q. Doctor, on that subject and in connection with some of Judge Lewis's questions, when we are talking about harmful, I am asking you, is pharmacological toxicity, or the pharmacological adverse reaction, the same as the issue of safety as you are using safety in describing the modality of using these plaintiff's products to treat the condition?

Mr. HOFFMAN. Object, Your Honor.

The COURT. He answered it, and I have summarized it for him,

and he has told me very clearly whether he makes it synonymous with it, even though it is harmless——

Mr. EPSTEIN. Okay.

The COURT (continuing). If it causes a doctor not to do what he might otherwise do, it then becomes harmful. That is his theory.

[149] By Mr. EPSTEIN:

Q. Dr. Spaet, during the course of the deliberation of the panel on hematology and drug efficacy study that you were a member of for the NAS NRC, was there general discussion among the panel members, or was there consideration of the uses of bioflavonoids in the treatment of bleeding states in man?

A. There was.

Q. During the course of that consideration, or the deliberations that you had, did you find any evidence of the efficacy for any bleeding states in man of these bioflavonoid products?

A. We did not.

Q. Or of the plaintiff's bioflavonoid products in particular?

A. We did not.

Q. When you say "we", you mean yourself and the rest of the panel members?

A. The remainder of the panel, I think that in retrospect now, I could talk about the panelists as other experts in the area with whom I specifically discussed these bioflavonoids.

Q. Would you give us their names, if you remember them, Dr. Spaet?

A. I can, some of them.

The COURT. I will concede he discussed it with [150] all the members of the panel.

* * * * *

RECROSS EXAMINATION

By Mr. HOFFMAN:

* * * * *

[151] * * *

Dr. Spaet, [152] on Exhibit C, page 4, to which Mr. Epstein referred you, am I correct in my recollection that you began reading about a third or so of the way down the page, the phrase beginning "Habitual and threatened abortion"?

A. Yes.

Q. And was it your testimony that you thought that was labelling that suggested that the products involved were being recommended for habitual and threatened abortion, and so forth?

A. That is right.

Q. I wonder if you would please read from the top of that page so as to put that last clause of the sentence in context, beginning "To help correct"?

A. "To help correct"—Do you want me to read it aloud?

The COURT. He does not need to read it. I can see it right here.

Mr. HOFFMAN. Fine, then.

The WITNESS. Okay.

Mr. HOFFMAN. I just wanted to direct the Court's attention to the fact that Dr. Spaet's testimony was reading part of a sentence out of context.

* * * * *

[154] REDIRECT EXAMINATION

By Mr. EPSTEIN.

Q. Doctor, did you tell us when you first started the survey of the literature concerning bioflavonoids?

A. It was in the early 1950's, that is that the bioflavonoids were caught up in my literature search net.

Q. And you saw the literature at that time?

A. Oh, yes.

Q. And reviewed it?

A. Yes. Maybe 1949.

The COURT. Do I understand, so that there will not be any misunderstanding, these bioflavonoids, not necessarily this one, because I think the record here reflects to 1962, as far as this information came out, but were comparable products in this general field, with, maybe, some minor additions, you know, to make it a little different, like Bayer's aspirin and somebody else's aspirin, have they been in common use in the medical field since when, 1949 or——

The WITNESS. About that, somewhere around there.

* * * * *

[159] [Milton Corn was called as a witness, and having been first duly sworn, was examined and testified as follows:]

By Mr. EPSTEIN:

* * * * *

[165] * * *

Q. Coming back specifically to the plaintiff's product, C.V.P. capsules, Doctor, is it your opinion that the administration of C.V.P. capsules to a patient who has the condition or is suffering from postpartum bleeding, is a safe modality for the treatment of that condition?

A. I don't believe it is.

Q. Why not?

The COURT. I do not want to get into this unless I have to, but isn't the only issue we are determining whether this was a new drug introduced in the market in 1962 and whether, as a result of it, it is covered by the grandfather clause? Isn't that the only thing we are going to decide here on this case?

Mr. EPSTEIN. Yes, but, Your Honor——

* * * * *

[177] * * *

By Mr. EPSTEIN:

Q. Dr. Corn, on October 9, 1962, did you know about bioflavonoids?

A. Yes.

Q. On October 9, 1962, did you have an opinion about the use of bioflavonoids for the treatment of bleeding conditions?

[178–199] Mr. HOFFMAN. Objection, Your Honor.

The COURT. Objection is overruled.

I mean the record is clear that you've got opinions on both sides, so we will add his for one more.

Mr. HOFFMAN. He is not talking about the product in this case, Your Honor.

The COURT. No, but we are talking about—We are going to put the product in this category. He is talking about general.

The WITNESS. Yes.

The COURT. Go ahead.

[200] By Mr. EPSTEIN:

Q. What was that opinion, Dr. Corn?

A. That it was medically ineffective and had no indication of which I was aware of for use in sick people.

The COURT. In other words, you go farther than the other. You say it has no medicinal value for any purpose period.

The WITNESS. That is my opinion.

The COURT. All right.

By Mr. EPSTEIN:

Q. Dr. Corn, coming to today, is that your opinion today also about the bioflavonoids?

A. Yes, it is.

Q. Is that opinion shared by your colleagues?

A. Insofar as I know.

Q. And is the opinion that you specified to me that you held on October 9, 1962, to the best of your recollection, was that opinion also held by your colleagues then?

A. Yes, as far as I know.

Q. Doctor, coming to the specific products of the plaintiff's drugs, are C.V.P. CAPSULES a bioflavonoid product?

A. Yes, they can be.

The COURT. I thought it was conceded they were.

Mr. EPSTEIN. Yes.

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[211] * * *

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Mr. EPSTEIN. Then to that extent I would then ask him the same question is it a safe modality to give C.V.P. capsules to a patient who would be suffering from postpartum bleeding, and I ask for your answer.

The WITNESS. No, I don't think it is.

The COURT. Tell me, doctor, to get—to get to the nub of it—Dr. Spaet told me—Why isn't it safe? Why isn't it safe? He is asking you if it is safe to give it to them. Medically why isn't it safe?

The WITNESS. The same type of reasoning that was brought out this morning.

The COURT. Yours is predicated on the same basis——

The WITNESS. Yes.

The COURT (continuing). Because it in your opinion keeps a doctor from giving him something that is better?

The WITNESS. That's right.

The COURT. It is not unsafe to give a bleeder a glass of water, is it?

The WITNESS. No, it isn't.

The COURT. Nor an aspirin, is it?

The WITNESS. Not usually.

[212] The COURT. All right. So now I am not saying that a bleeder you ordinarily wouldn't give aspirin——

The WITNESS. Right.

The COURT (continuing). But you wouldn't say it is harmful or unsafe.

So let's get to the nub of this case. We are not getting anyplace.

I understand your argument. You don't need any more evidence to convince me of your argument. Whether I will buy it or not is another story. And their argument is that since this, conceding it is harmless, like water, since the doctor is taken in by believing that it's going to give some positive effect, it becomes harmful because it keeps the doctor from giving what you say he ought to give them. Isn't that right?

The WITNESS. That's right.

The COURT. All right. I understand your logic.

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[214] * * *

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By Mr. EPSTEIN:

Q. Doctor, I want to ask, if I may quote to you the following statement and ask you whether you agree or disagree with it:

"The high hopes once held out for the flavonoids as important metabolites have not materialized. Instead present knowledge indicates that while they possess mild pharmacological properties under certain conditions the flavonoids have no known nutritional functions. They cannot——"

The COURT. No, known what?

[215] Mr. EPSTEIN. No known nutritional functions.

The COURT. We are getting in the class with Post Toasties now, aren't we?

Mr. EPSTEIN. I hope not, your Honor.

The COURT. I read something about they have no nutritional value too.

Mr. EPSTEIN. That will be a new one before you at some later time.

"They cannot be regarded as essential nutrients. Those workers who claim therapeutic value for the flavonoids have not

supported their claims with data obtained from well-controlled clinical studies. Until such studies are made, it must be concluded that the flavonoids are of little or no value in the treatment of disease."

By Mr. EPSTEIN:

Q. Do you agree or disagree—I'm sorry—If I may, doctor, I will put it before you.

A. Well, I read what you read.

Q. And ask you again, renewing my question, do you agree or disagree with that statement?

A. I agree.

Mr. HOFFMAN. Mr. Epstein, are you offering that statement that you just read in as proof in itself of the matter?

The COURT. No. It is evidence of what that [216] author said. That doesn't make it a fact. That is his opinion.

Mr. EPSTEIN. And I am offering it as the opinion of Dr. Corn which he just stated the view contained therein.

The COURT. It is Dr. Corn's opinion insofar as the part he agrees with.

Mr. EPSTEIN. Yes, sir.

By Mr. EPSTEIN:

Q. Now Dr. Corn, is the statement that is—Yes, sir.

A. Well, I agree with everything except the fact that high hopes were once held. I don't know who held the high hopes.

The COURT. I would agree with that. If they held high hopes I would want to know what they were and when they dropped.

The WITNESS. They weren't mine.

The COURT. What?

The WITNESS. They weren't mine.

The COURT. They must at one time because——

The WITNESS. Someone must have.

The COURT (continuing). According to this expert they had high promise for medicinal purpose; isn't that right?

The WITNESS. Yes.

[217] The COURT. The test ought to show what the negative responses were and that article doesn't prove much, does it? It is in generalities, isn't that correct, doctor? It just says the high hopes, it doesn't live up to high hopes. What does that mean?

Mr. EPSTEIN. Your Honor, since it is in evidence I didn't quote to him the whole thing. There is a four-page document.

What I asked the doctor's opinion on was the summary or in effect conclusion to this article.

The COURT. He said he read all of it but he doesn't agree with the first premise so that just drops it all.

I mean you have nullified it by a single statement. If his premise is wrong his conclusion is wrong. So he says the premise it had high hopes he cannot agree with it.

By Mr. EPSTEIN:

Q. But I do understand you to say, Dr. Corn, that except for that sentence you do concur with the statement?

Mr. HOFFMAN. Object to the leading question, your Honor.

The COURT. It doesn't make any difference.

Let's get on with it.

He agrees with it.

The WITNESS. I agree with that, and I simply don't know whose high hopes these were, but the remainder of [218] the statement insofar as it refers to the actual value and the data pertaining to flavonoids I agree with completely.

By Mr. EPSTEIN:

Q. Doctor, is it your opinion that the administration of the plaintiff's C.V.P. capsules to a patient who is suffering from hypertension would be a safe modality for the treatment of that condition?

Mr. HOFFMAN. Objection, your Honor. The same grounds as before.

The WITNESS. No.

The COURT. Let it in. His answer is going to be no.

The WITNESS. Yes.

No.

By Mr. EPSTEIN:

Q. Would you tell us why, doctor? Would you tell us why it would not be a safe modality, Dr. Corn?

The COURT. He says that all of his safety is predicated on the fact that it keeps the person from getting a safe or better product.

The WITNESS. That is quite right. Hypertension can kill people, and I think the doctor taking care of hypertension has considerable responsibility to treat it just as intelligently and

as quickly as he can, and I think that any time loss or waste, whether it is two months, two weeks or [219] two minutes on an inefficient or inefficacious remedy is not only valueless but prejudicial to the health of the patient.

The COURT. Let me ask you this, doctor.

The WITNESS. Yes.

The COURT. Are placebos valueless to the medical profession?

The WITNESS. No. They are of considerable value if used correctly.

The COURT. I say that many doctors think they are necessary, don't they?

The WITNESS. Yes.

The COURT. And a placebo is apparently in the category with this pill, according to you. It has neither nutritional nor medicinal value but it doesn't harm much, so it is in the category of the placebo. Is that right?

The WITNESS. It is except for the intent in its use.

The COURT. You give placebos for a lot of things, don't you?

The WITNESS. Yes. * * *

[221] * * *

By Mr. EPSTEIN:

Q. I will ask you, doctor, if your opinion that you [222] have just enumerated that you just discussed with me as to the bioflavonoids today, was that your opinion, did you hold the same opinion on October 9, 1962?

A. Well, yes, I am sure that it would have been.

The COURT. I take it so whatever it is germane, from your standpoint, doctor, they never were worth anything.

The WITNESS. That's right, Judge. That is exactly my feeling.

The COURT. Now I will go further than you did.

Mr. EPSTEIN. Fine, sir.

The COURT. You never recognized them as being medically worth a bottle.

The WITNESS. That's right.

Mr. EPSTEIN. Fine.

I have no further questions on direct, sir.

The COURT. All right.

Mr. HOFFMAN. Your Honor, I hope to be much briefer than we were with Dr. Spaet.

CROSS EXAMINATION

By Mr. HOFFMAN:

Q. Dr. Corn, I believe you testified that you were unacquainted with the plaintiff's C.V.P. products involved in this case until five or six months ago; is that correct?

A. Yes, Mr. Hoffman.

Q. And you testified that in October of 1962 [223] you were familiar with other bioflavonoids products, is that correct?

A. Bioflavonoids in general.

Q. Could you enumerate the ones with which you were familiar?

A. No, and this is the point that was brought up before. If in fact one is thinking about a class of compounds, it isn't necessarily—it doesn't necessarily mean that I know or even need to know every specific commercial source of such, and I am not sure—if that is what you're getting at.

Q. I am asking if you do know, if you can identify any particular, as you put it, commercial source of the product that you consider a bioflavonoid in the same class as plaintiff's C.V.P. product?

A. No, I cannot, and the reason being that all the information I had ever received or had in fact read about had left me with the opinion I expressed here today. Since I have never felt the need under any circumstances to use this on a patient it was never necessary for me to find out who was making it.

The COURT. Let me get at it this way, doctor.

Personally you have never used one?

The WITNESS. Never.

The COURT. You don't know of any doctor who has ever used any?

[224] The WITNESS. I personally have never met a physician who has used it.

The COURT. Therefore you obviously from experience could know nothing about it except what you read?—

The WITNESS. That is quite right.

The COURT. All right.

Does that answer all your questions?

Mr. HOFFMAN. Almost, your Honor.

The COURT. He knows very little about it. I will tell you.

By Mr. HOFFMAN:

Q. Do you know, can you tell us, what the ingredients are in C.V.P. capsules?

A. Well, I can read the label, as you did. It said it is a citrus of bioflavonoids——

Q. Compound?

A. Compound and it also contains a hundred milligrams of Vitamin C.

Q. Is it your understanding that all the products that you would consider in the bioflavonoid class contain citrus bioflavonoid compound.

A. No. Bioflavonoid compounds can be obtained from a variety of plants and fruits.

Q. So then you have no particular reason to think, is that correct, that the C.V.P. capsules do in fact have the [225] same ingredients as the products that you were familiar with in 1962?

The COURT. He says he is not familiar with any products. He is only familiar with the general subject matter that he has read. That is what the doctor said.

Mr. HOFFMAN. Let me reframe the question then.

The COURT. And he knows no doctor who has ever used one.

By Mr. HOFFMAN:

Q. What is your reason to think, Dr. Corn, that the ingredients of C.V.P. capsules are the same in relevant respect as these other bioflavonoids with which you were familiar in 1962?

A. Since I think it is a generalization of the class of bioflavonoids that they have such and such action or not such and such action, and I think someone who feels that he has some special subgroup of bioflavonoids compounds that can do something has in fact got the burden of demonstrating this. Simply saying, that you have citrus bioflavonoid compounds tells me neither one way nor the other, whether your compound is specifically different or similar to.

Q. In other words, you cannot tell, there may be a difference, you can't say that they are the same; is that correct?

The COURT. You are arguing with him now. He [226] has told me; what he knows about them.

Mr. HOFFMAN. I would like to get the witness to say whether or not he believes that all bioflavonoids are necessarily the same or whether differences among them might result in differences.

The COURT. He says they aren't the same. One comes from an orange, one comes from a lemon, one comes from a vegetable, plus other articles; isn't that right?

Mr. HOFFMAN. There may be differences. That is right.

The COURT. So they obviously couldn't be identical.

By Mr. HOFFMAN:

Q. Dr. Corn, have you ever considered a difference between water soluble by a flavonoid and insoluble by flavonoids?

A. Yes, I have considered it in the sense of thinking about it and have noticed the distinction in some standard pharmacology description of these agents.

Q. Do you know into which group C.V.P. capsules fall?

A. I know that there is a statement made by the makers that it falls under the water soluble group.

Q. Can you tell us whether any of the bioflavonoid products with which you were familiar in 1962 also fell into [227] that group?

A. I cannot.

Q. Dr. Corn, directing your attention to Defendant's Exhibit D, which is the article——

A. Yes.

Q. What was the date—no—this is the one Dr.—Mr. Epstein gave you?

A. Yes.

Q. What is the date on that article?

A. 1957.

Q. Do you know whether or not any studies on bioflavonoids have been done since that article?

A. Quite a large number.

The COURT. What was the answer?

The WITNESS. Yes, a number of studies have since 1957.

The COURT. He didn't ask you. There must be a reason. What do they show?

Mr. HOFFMAN. We hope to get to that if the day holds out, your Honor.

The COURT. All right.

Mr. HOFFMAN. We don't think this witness is the vehicle.

The COURT. If he knows.

Do they hold the same position as this one, [228] these other studies that you have seen?

The WITNESS. No.

The COURT. What do they hold? What do they—what is the difference if you know?

The WITNESS. Yes. There is a variety of studies, many of them reports by people who feel that they used it in a group of patients and it helped some of them.

The COURT. All right. So there are some favorable subjects.

The WITNESS. There are some, yes.

The COURT. He recognizes that there are some that are favorable.

Go ahead.

But he has a right to his opinion.

By Mr. HOFFMAN:

Q. Dr. Corn, does that article, Exhibit D, deal with C.V.P. capsules or duo-C.V.P. specifically?

A. I don't believe so.

Q. Do you know, if you know, whether any of the later studies to which you refer, which you have just discussed with the Court, do deal with C.V.P. or duo-C.V.P. specifically?

A. Yes, some of them do.

Q. Dr. Corn, directing your attention to the stipulated exhibits, what has been called here the label, directing [229] your attention to Exhibit C, the fourth page of that exhibit—do you have it?

A. I think so. This is the picture?

Q. No. The fourth page. It is numbered four on the bottom. Keep going.

A. Oh, I see. Yes.

Mr. HOFFMAN. Excuse me a moment, your Honor.

Your Honor, I think that I prefer to withdraw this line of questioning.

The COURT. All right.

Mr. EPSTEIN. I'm sorry. I didn't hear what you said.

Mr. HOFFMAN. I said I prefer I think to withdraw this line of questioning and it will not be necessary to refer to the labels.

The COURT. All right.

Do you have any further questions?

Mr. HOFFMAN. No further questions, your Honor.

Mr. EPSTEIN. I have two questions I want to ask him, if your Honor please?

The COURT. All right.

REDIRECT EXAMINATION

By Mr. EPSTEIN:

* * *

[231]

* * * * *

The COURT. All right.

[232] They have rested.

Do you have any rebuttal?

Mr. HOFFMAN. Yes, we do, your Honor.

The COURT. All right. Call the first witness.

Mr. HOFFMAN. Dr. Karpman, please.

Whereupon,

[Harold L. Karpman was called as a witness and, having been first duly sworn, was examined and testified as follows:]

Mr. HOFFMAN. Mark this as Plaintiff's Exhibit 5 for identification.

(Dr. Karpman's curriculum vitae was marked for identification as Plaintiff's Exhibit No. 5.)

DIRECT EXAMINATION

By Mr. HOFFMAN:

Q. Doctor, would you please state your name and address for the record?

A. Harold L. Karpman, 465 North Roxbury Drive, Beverly Hills, California.

Q. What is your profession?

A. I am a physician.

Q. What position do you hold, doctor?

A. I am chief of the Peripheral Vascular Laboratories of the Cedars-Sinai Medical Center, assistant clinical professor of medicine, Southern California School of Medicine, [233] president-elect of the American Thermographic Society, fellow of the American College of Physicians, the American College of Cardiology, the American College of Chest Physicians, the International College of Angiology, the American College of Angiology.

Mr. EPSTEIN. Your Honor, we are willing to stipulate the curriculum vitae.

The COURT. He has a very extensive one.

I always wondered sometimes when these doctors belong to all these societies how they get any time to practice medicine.

Mr. HOFFMAN. They are too busy determining the concensus, your Honor.

The WITNESS. We work long hours like judges.

The COURT. What?

The WITNESS. We work long hours like judges.

The COURT. I see.

No, I'm just being facetious.

The Court rules the doctor is well qualified and he is an expert and may give an opinion in his field of medicine if he be advised.

Go ahead.

Mr. HOFFMAN. We move the admission of the curriculum vitae which is marked as Plaintiff's Exhibit 5.

The COURT. Let it be admitted.

[234] (Plaintiff's Exhibit No. 5, heretofore marked for identification, was received in evidence.)

By Mr. HOFFMAN:

Q. Doctor, are you affiliated with a major hospital? I believe you named one.

A. Yes.

Q. Could you repeat that?

A. I didn't name them. I am affiliated with Los Angeles County Hospital, Cedars-Sinai Medical Center, Saint Vincent's Hospital in Los Angeles.

The COURT. Do you consider those major hospitals?

A. Yes, they are very major hospitals.

Q. Are you acquainted with the C.V.P. products manufactured by the plaintiff in this case?

A. Yes, I am.

Q. Which ones?

A. Duo-C.V.P. primarily.

Q. Are you familiar with C.V.P.?

A. Yes.

Q. Could you tell us the circumstances in which you became familiar with it?

A. In 1957 during the course of my training I became involved in the study of the vascular diseases as well as cardiology and my interests in agents that would affect the [235] vascular problems started at that time.

Q. Have you used C.V.P. or duo-C.V.P. in your practice?

A. Yes, I have.

Q. Do you now?

A. Yes.

Q. In the course of your studies have you had occasion to become familiar with the scientific literature in the field of bioflavonoids?

A. Yes.

Q. Have you become familiar with the scientific literature specifically on C.V.P. and duo-C.V.P.?

A. I am certain not all of the literature but a great deal of it.

Q. Have you discussed C.V.P. and duo-C.V.P. with other experts in the field?

A. Yes, I have.

Q. Can you give us some names and dates?

A. Yes, I can. I started discussing duo-C.V.P. in 1960 or '61 with a number of physicians in preparation for a project that I was going to conduct. The names are Milton Gottlieb, M.D., Ronald Okun, M.D., Travis Winsor, M.D., Isadore Ferrie, M.D., Sidney Wiseman, M.D. There were a number of them.

Q. Have you ever heard of any adverse reports with [236] respect to the safety of C.V.P. or duo-C.V.P. when used in treating abnormal capillary permeability or fragility?

A. Absolutely never.

Q. Have you ever read of any such adverse reports?

A. Never.

The COURT. So to save you time, I haven't heard any testimony of any adverse effects other than reaching an adverse effect by saying by being lulled into using it the patient doesn't get the benefit of something he ought to have.

Let's get in on that deal.

Mr. HOFFMAN. Fine.

By Mr. HOFFMAN:

Q. Do you have an opinion, doctor, whether on October 9, 1962, qualified experts generally recognized C.V.P. and duo-C.V.P. as safe for use in bleeding states associated with capillary, abnormal capillary fragility and permeability?

A. Yes, I do.

Q. What is that opinion?

A. At that time and at the present time I have never heard any qualified expert until today say that duo-C.V.P. or C.V.P. was in any way potentially harmful.

Q. Then if I understand you correctly, moving to my next question, in fact, your opinion today is that today qualified experts generally recognize C.V.P. and duo-C.V.P. as safe for use in the conditions recommended in the label?

[237] A. Absolutely.

Q. Have you reviewed the labeling of the products C.V.P. and duo-C.V.P.?

A. Yes, I have reviewed it, yes.

Q. Doctor, what is your understanding of the conditions for which C.V.P. and duo-C.V.P. are offered?

A. Abnormal capillary fragility or ulcered capillary permeability.

Q. Doctor, I would like to show you the famous exhibits A through K, and specifically direct your attention to page four of Exhibit C. Is it your opinion, doctor, that a physician would understand that labeling to recommend the product for use in the underlying conditions?

Mr. EPSTEIN. Objection, your Honor. I think he can testify as to his understanding of it as Dr. Spaet did this morning, but not as to what the general state of some physician's mind might be.

The COURT. Objection is overruled. I allowed Dr. Spaet. He said the average doctor to him would read it thus and thus. I will let this doctor say the same thing.

The WITNESS. As I read this and the following pages of this brochure, it is very clear to me that the brochure was attempting to point out the results of research studies that had been collected and had been published in a brochure and that these are simply quoting what the research [238] studies and summarizing what the research studies had indicated. Whether anyone agrees with the research studies or not, these are simply quotations from those studies. When they have the little thirty-one and forty-six things, it means they are referring to specific paper, a specific research study.

The COURT. That is a footnote that supports it.

The WITNESS. In the back of the document they usually have fifty research studies, one, two, three, four, five.

The COURT. I understand.

The WITNESS. And each number is assigned to a specific individual, and this is a summary of those studies.

By Mr. HOFFMAN:

Q. Doctor, just to clean up the record, has your familiarity with the scientific literature continued since October 9, 1962?

A. Yes.

Q. Has your familiarity with the opinions of qualified experts continued since 1962?

A. Yes.

Q. So that the testimony you have recently given with respect to your opinion as to the opinions of qualified experts in 1962—I'm sorry—is the same for 1962 and [239] today?

A. I said yes. I thought they were exactly the same.

Q. Thank you.

Doctor, in your opinion, is it your opinion that the views of qualified experts, either in October 9, 1962 or today, would be that a lack of effectiveness for C.V.P. or duo-C.V.P. in treating abnormal capillary permeability and fragility would be regarded as presenting a safety question? Let me reframe that. I think I garbled it.

Is it your opinion that the opinions of qualified experts in 1962 and today are that a lack of effectiveness for C.V.P. in treating abnormal capillary permeability and fragility would be regarded as presenting a safety question?

A. I think it in no way presents a safety problem.

Q. Is it your opinion that the opinions of qualified experts would be the same?

A. Yes.

Mr. HOFFMAN. I have no further questions.

The COURT. Doctor, so that I will thoroughly understand you, I understand that you studied this subject matter and particularly these particular drugs in question here and that you have used them in your practice and know other doctors who have used them over a long period of time; [240] is that correct?

The WITNESS. Yes, sir.

The COURT. Based on your medical experience in the cases that you have used on your own and in experiences of other

doctors that you personally know about, have they had a positive effect for affecting this capillary situation that is referred to?

The WITNESS. I think they have had a positive effect in certain measured cases. The problem is, as was not really gone into this morning, frequently we look at the end result of the problem. I think one of the important things to distinguish in any agent is the difference between treating a symptom and treating a disease. Capillary fragility is a symptom of disease. You want to treat both things. If they had a symptom of brain tumor you want to treat the pain as well as the brain tumor.

The COURT. You can have headaches without having a brain tumor.

The WITNESS. Yes, sir.

The COURT. Don't give me that symptom.

The WITNESS. What I mean is because you may have a brain tumor doesn't mean you shouldn't treat the headache. And by the same token if you have capillary fragility and duo-C.V.P. is effective in improving capillary fragility it doesn't——

[241] The COURT. Do you mean it has a positive effect in your experience based on your experience with the product?

The WITNESS. Yes, it has.

The COURT. And in the treatment of the symptom?

The WITNESS. Yes, it has, in selected cases, absolutely.

The COURT. In no case as far as your knowledge is concerned has it had an adverse effect, a harmful effect?

The WITNESS. Not only in my personal knowledge but I have never heard of a harmful effect.

The COURT. You heard of some this morning.

The WITNESS. I did not. What I heard was that someone wasn't treating——

The COURT. You heard it was harmful if you use this and, therefore, did not use what you ought to have used and you died as a result of not using what you ought to have used; therefore this becomes harmful.

The WITNESS. But, sir, that line of reasoning is like saying you shouldn't give kaopectate for diarrhea, if a serious illness is causing it. You still treat the symptom as well as the illness.

The COURT. You do it anyway.

The WITNESS. You treat both the things. When you treat the symptom you still look for the cause of the illness and you shouldn't negate looking for the cause.

[242] The COURT. All right. I understand your position. I just wanted to get it.

All right. Thank you.

Mr. HOFFMAN. Your Honor, could I follow up on that with one question?

The COURT. Yes.

By Mr. HOFFMAN:

Q. Doctor, directing your attention again to the labeling and, rather, the exhibits that are before you, without attempting to characterize them as labeling, you have reviewed those prior to your appearance here this morning, is that correct? Is that true?

A. Yes.

Q. Is there anything in those exhibits, doctor, which says to you either expressly or by implication that C.V.P. or duo-C.V.P. or for that matter any of the products covered by those documents are to be the exclusive therapy in any given situation?

A. Nothing that I can recall.

Q. Nothing that you can recall. Would you like to take as much time as you care to go through with it?

The COURT. I will not give him that much time to read it all. You know it doesn't purport to say exclusive. They don't claim it does. You people keep putting up straws [243]—straw-men and then knocking them down.

Mr. HOFFMAN. We heard it from Dr. Spaet, your Honor. I just wanted to cover it. We will be satisfied with that.

I have no further questions.

The COURT. All right.

Whichever one of you want to examine this doctor.

CROSS EXAMINATION

By Mr. EPSTEIN:

Q. Doctor, you indicated that you used C.V.P. in your practice?

A. Yes, I have, sir.

Q. Would you tell me, doctor, what percentage of your current practice is devoted to seeing patients on a day-to-day basis? How many a patients a day do you see, doctor?

A. There are some days when I'm not in the office, but as a rule anywhere between ten and forty a day.

Q. Doctor, you indicated that your interest and your curriculum vitae indicates that your special interest is in cardiovascular diseases?

A. Yes, sir.

Q. Are you a specialist in hematology?

A. No, I am not a specialist in hematology. I am a specialist in cardiovascular diseases.

[244] Q. Are you board certified in hematology?

A. No, I am not.

Q. You talked about the fact that you didn't think that these drugs were potentially harmful. In the course of your practice on a day-to-day basis, the patients that you see, do you see patients who have a condition of habitual and threatened abortion?

A. No, I don't.

Q. Do you in that case, can you tell me on what basis you would recommend the use of C.V.P. in that kind of a situation, doctor?

A. I would recommend it in the way that I know that some medicologists have used it.

Q. No, I'm asking for your opinion.

The COURT. No. Let him answer it. He recommended it the same as he knows his own knowledge that some gynecologists have used it and the gynecologists feel in this subject matter.

Let him answer it.

The WITNESS. I practice in a very sophisticated area. I have doctors who are specialists in the hospitals that we use, and I know that many physicians who are looking for habitual abortions will look through all the medical causes they can and frequently not finding them will treat for a cause or treat any way they can to make the abortions discontinue. [245] I don't see patients with this problem because when I see them I refer them to a competent gynecologist who has more competency in the matter than I have.

By Mr. EPSTEIN:

Q. Do you treat patients on a day-to-day basis that you see for postpartum bleeding?

A. No.

Q. Do you treat patients for epistaxis?

A. Occasionally.

Q. About how many, doctor?
A. How many in what period, sir?
Q. In a month.
A. In a month, maybe two or three.
Q. Do you treat patients who have had tonsilectomies?
A. No.
Q. Do you treat patients who have hypertension?
A. Yes.
Q. Do you treat patients who have little strokes?
A. Yes.

The COURT. Get me that—just to—I am getting a lot of medical education—but what has hypertension got to do with bleeding?

The WITNESS. Are you asking me, sir?

The COURT. Yes.

[246]

The WITNESS. It has to do—There are a number of areas where hypertension is very important to bleeding. For example, people who have hypertension can develop bleeding intra-cerebrally and can develop strokes on that basis.

The COURT. Bleeding follows from it but hypertension is not bleeding, is it?

The WITNESS. No, absolutely not, but I think one of the points——

The COURT. You mean that is one of the residuals?

The WITNESS. That's one of the residuals of hypertension. Hypertension itself——

The COURT. Hypertension itself has nothing to do with bleeding.

The WITNESS. No. Hypertension itself is harmless. The problem with hypertension is the complications of it.

The COURT. You mean what follows from it?

The WITNESS. What follows from it.

The COURT. And what causes it.

The WITNESS. What causes it.

Mr. HOFFMAN. Your Honor, if I may be heard, I think what Mr. Epstein is now attempting is to attack the qualifications of this witness.

[247] The COURT. I think he has a right to do that.

Mr. HOFFMAN. I thought he stipulated to the qualifications when we first got it out.

The COURT. He stipulated he was an expert, and I have ruled that he is but all experts are not equally qualified. Obviously it

is a proper way to find out what he knows. This doctor seems to be doing very well handling himself.

By Mr. EPSTEIN:

Q. Doctor, do you treat patients with diabetic retinitis?

A. With a diabetic retinopathy, I do.

Q. How about a diabetic retinitis?

A. Is there a difference?

Q. I would ask you: Is there a difference?

A. Retinopathy means the general illness, a diabetic inflamation of the back of the ear. Retinis means acute inflamation. If I had someone who had acute inflamation——

The COURT. Acute means present.

The WITNESS. Real sudden onset, your Honor, diabetic retinitis, but retinopathy is a general term.

You can use diabetic retinitis on chronic cases where it has been present for a long period of time. Yes, those patients I do treat.

[248] By Mr. EPSTEIN:

Q. Do you treat those patients regularly with C.V.P. products?

A. Not regularly, no.

The COURT. Do you use those products with these type of patients?

The WITNESS. Have I used it? Yes, I have, sir.

The COURT. With harmful or positive effects?

The WITNESS. Never with a harmful effect. I have never seen a harmful effect with duo-C.V.P. in my life.

The COURT. I am talking about the patients you used on this particular ailment that he is talking about.

The WITNESS. None, no, sir.

The COURT. Did it have any positive effect?

The WITNESS. Yes, on occasion.

The COURT. All right.

By Mr. EPSTEIN:

Q. Did the diabetic—Did the retinitis go into remission or become cured as the result of the use of C.V.P., doctor?

A. I would say that it did not progress on the cases I used it on.

The COURT. Aren't we getting way afield? I thought if you had diabetes that you never got cured. I [249] thought rest was the very best. Am I very wrong about that?

Mr. EPSTEIN. No. We're talking about diabetic retinitis, sir. I'm sorry.

Mr. HOFFMAN. Your Honor, I thought we were talking about capillary fragility and permeability.

The COURT. We have covered everything in the medical horizon.

By Mr. EPSTEIN:

Q. Do you treat patients with menorrhagia?

A. Not complex. If it is simple, I do. Usually if there is any problem that persists I refer to a gynecologist.

Q. Do you regularly treat such patient with C.V.P. products?

A. On occasion.

Q. Do you regularly treat them with C.V.P. products?

A. No. On occasion, I said.

Q. Do you treat patients with rheumatoid arthritis?

A. Yes.

Q. Do you regularly treat patients on a regular basis with rheumatoid arthritis?

A. Yes.

Q. Do you treat patients who have hemorrhagic [250] duodenal ulcers?

A. Yes.

Q. Do you see them regularly?

A. Yes.

Q. Do you treat such patients regularly with C.V.P. products?

A. No. I treat none of them with C.V.P. products.

Q. How about hemorrhagic cysitis? Do you treat patients that have hemorrhagic cystitis?

A. No. I see them on occasion but I don't treat it.

Q. What do you do with those patients?

A. I refer them to a proper urologist.

Q. Do you give them C.V.P. products when they are in your office before you refer them to a urologist?

A. No.

Q. Do you use C.V.P. products at all on such a patient?

A. I have not used them on that particular brand of patient.

Q. As to post-operative bleeding, I assume that you have surgery from time to time—do you deal with patients who have post-operative bleeding?

A. Do I see patients with post-operative bleeding?

Q. Yes.

[251] A. Yes, I do.

Q. Do you see patients that have post-operatives bleeding as a regular course with a C.V.P. product?

A. No.

Q. As to radiation therapy, do you see any patients that require radiation therapy.

The COURT. Do you contend—You're getting awfully far—I don't object—this doctor, as I say, seems to be very broadly based as far as his experience is concerned. But post-operative bleeding is major bleeding basically from a surgical standpoint. Do you contend that these pills are——

Mr. EPSTEIN. Well, your Honor——

The COURT. Wait a minute. Do you contend that a surgeon with post-operative bleeding would put somebody on some bioflavonoid with Vitamin C or X or K?

Mr. EPSTEIN. I'm not a doctor, and I'm reading it, and it says here in Exhibit C in bold letters "post-operative bleeding," and it says underneath in bold letters in one sentence "But administered pre-post-operatively, C.V.P. had a salutary effect on capillary bleeding and hastened healing following surgical procedures."

All I can say to you is that I will submit on my own course I don't want any doctor to give me C.V.P. if I have post-operative bleeding.

* * * * *

[253] * * *

REDIRECT EXAMINATION

By Mr. HOFFMAN:

* * * * *

[255] * * *

Q. Doctor, you aren't a hematologist, are you?

A. No, I'm not.

Q. What is your specialty?

A. I am a specialist in cardiovascular diseases.

Q. Do you consider that hematology is the only specialty whose members are experts qualified to evaluate the safety or effectiveness of drugs such as C.V.P. or duo-C.V.P.?

A. Absolutely not.

Q. Do you believe that your specialty is such a specialty?

A. Of course I do. You're dealing with——

The COURT. You wouldn't expect him to say no in either event.

The WITNESS. I can substantiate it easy by saying you are dealing with the pipe and the water in the pipe and it's the same

thing with the blood and the pipes that [256] carry the blood. You know they both involve the same thing.

The COURT. You handle the pipes.

The WITNESS. I handle the pipes and the heart, the pump, and the hematologist takes care of the stuff that goes inside.

The COURT. So you must know what goes through your pipes——

The WITNESS. Exactly.

The COURT (continuing). And he ought to know whether the pipe is rusty or not.

The WITNESS. Exactly. I will respect his opinion to a certain extent.

The COURT. All right.

Thank you.

Mr. HOFFMAN. No further questions.

The COURT. Step down.

(Witness excused.)

The COURT. Call your next witness.

Mr. HOFFMAN. Dr. Clemetson, please.

Whereupon,

[C. Alan B. Clemetson was called as a witness and, having been first duly sworn, was examined and testified as follows:]

(Dr. Clemetson's curriculum vitae was marked for identification as Plaintiff's Exhibit No. 6.)

[257] Mr. EPSTEIN. Your Honor, the defendant will stipulate the contents of the curriculum vitae of C. Alan B. Clemetson, M.D., that has been delivered to us, including attached thereto the bibliography of Dr. Clemetson to the items of twenty-three published papers.

The COURT. All right. Let them be admitted and I will accept the doctor as a very qualified expert in the medical field and let him testify accordingly.

The CLERK. Plaintiff No. 6.

Plaintiff's Exhibit No. 6, heretofore marked for identification, was received in evidence.)

DIRECT EXAMINATION

By Mr. HOFFMAN:

Q. Doctor, will you state your name for the record, please?

A. C. Alan B. Clemetson.

Q. Doctor, your curriculum vitae has been introduced into evidence. Can you tell us what your present professional position is?

A. I am director of the Department of Obstetrics and Gynecology at the Methodist Hospital in Brooklyn, and I am an associate professor at the Downstate Medical Center of the State University of New York.

Q. Do you consider these major hospitals and teaching institutions?

[258] A. Most certainly.

Q. Are you personally acquainted with C.V.P. and duo-C.V.P.?

A. I am. Not—I have only used the duo-C.V.P.

Q. Can you tell us the circumstances in which you became familiar with them?

A. In 1959 or '60, I was teaching at the University of Saskatchewan in Canada, and I conducted a study of the treatment of women who had excessive menstrual bleeding associated with capillary fragility, easy bruising and sometimes bleeding gums, and in this study we used both the genuine duo-C.V.P. and lactose placebo capsules which were double-blind labelled, one was labeled X and the other Y, and we didn't know at the beginning of the study which was which. All the patients had one month without any treatment, and I had a lady technician who would go every day to the patient's home to test the capillary strength, the skin of the arm with a suction machine. She would find out how many pads had got soaked and in some cases we used a measure of blood loss.

In this study there was no doubt whatsoever that eight out of ten of the women who had this kind of bleeding problem were improved by the product.

Q. Was this study ever published, doctor?

A. It was published in the American Journal of [259] Obstetrics and Gynecology in 1962.

Q. Do you use C.V.P. in your practice?

A. I do.

Q. For how long have you?

A. Since I first discovered its effectiveness in 1959 or '60.

Q. In the course of your studies and use of the duo-C.V.P. have you had occasion to become familiar with the scientific literature dealing with bioflavonoids?

A. Yes.

Q. And specifically with duo-C.V.P.?

A. Yes, I have.

Q. Have you discussed duo-C.V.P. with other experts?

A. Yes.

Q. Can you give us some names and dates, please?

A. Oh, I have spoken to so many people in France, in——

The COURT. It is not going to do any good to fill the record with names. I mean I will accept it if he says he discussed it with other doctors, certainly I will agree that he has.

I wouldn't expect him to tell me he had if he didn't.

He says he has. That is sufficient for me.

[260] By Mr. HOFFMAN:

Q. Doctor Clemetson, have you ever read or heard of any adverse reports on the safety of duo-C.V.P.?

A. Not until today. Well, that was not a report, but we had these statements that they might be dangerous which until this time I have never heard of anything to that effect, and I would say that they would probably be one of the safest of all drugs on the market today. They are mild. They are slow in effect. They take a month or two to have effect but the effect is beneficial always. I have never seen a harmful effect from this product and that is more than you can say for most of the drugs that the hematologists use which are very potent drugs which can kill if you double the dose.

Q. Doctor, let me direct your attention to the packet of materials, Exhibit Nos. A to K that I believe you have before you. Have you?

A. No, I have not read them.

Q. Have you seen these?

A. No, I haven't. I am familiar with the labeling.

Q. You are familiar with the labeling?

A. I have seen it in the past but I haven't read this stuff.

Q. Doctor Clemetson, would you say that your previous [261] comments as to not having read or heard of adverse reports on the safety of duo-C.V.P. would apply to the use of C.V.P. in the conditions in the labeling with which you are familiar as well as just generally?

A. Most of the implications of the labeling, that it is good for conditions associated—for the capillary fragility associated with various conditions I would agree with.

I must say I could not agree, I haven't read the labeling, I couldn't agree with the treatment of postpartum hemorrhage, which is in here. It seems to come up. I haven't seen it, but that I do not agree with. I mean I wouldn't treat a patient with postpartum hemorrhage with this. But I mean a patient with capillary fragility is a different thing altogether. I mean maybe they left a bit of placenta in and that is why she's got post-

partum hemorrhage. Nobody in their right sense is going to treat that.

Q. Doctor, directing your attention to the celebrated page four of Exhibit C, I wonder if you would read to yourself the material in bold face beginning with the words——

The COURT. What he is asking you, doctor, is to have you read the whole thing, the headlines at the top and then this part which does refer to this postpartum.

The WITNESS. I mean I take objection to the postpartum. I am not going to be associated with that.

[262] I think for the use of threatened abortion or recurrent abortion, I have read Javits' work on this, I have read Greenblatt's work on this, and although I haven't conducted a controlled study myself I have found it useful for this purpose.

By Mr. HOFFMAN:

Q. For controlling abnormal capillary fragility and permeability?

A. Associated with this threatened abortion.

Q. Doctor, do you have an opinion whether on October 9, 1962, qualified experts generally recognized that C.V.P. products were safe for use in the conditions you have just mentioned?

A. Their safety was never questioned. Their efficacy, yes. Efficacy has been questioned, but safety, never.

Q. Doctor, do you consider that the use of duo-C.V.P. in treating the conditions you have mentioned would be unsafe by reason of an alleged lack of effectiveness?

A. No. I think this is a specious argument.

Q. Do these opinions that you have expressed as to the state of expert opinion in 1962 apply, in your opinion, apply to the state of expert opinion today?

A. What I just said?

Q. Yes.

[263] A. I think this is true today, just as it was then.

The COURT. All right.

Do you have any questions?

CROSS EXAMINATION

By Mr. EPSTEIN.

Q. Doctor, you made a statement that hematologists used drugs that a double dosage could kill. What kind of drugs were you referring to that hematologists use?

A. I was thinking of dicoumeral. The Food and Drug Administration is particularly interested in drugs which have a demonstrable pharmacological affect, such as the drug like dicoumeral which will half the clotting time of the blood, and if you double the dose you kill the patient. This is perfectly safe according to the F.D.A.

Q. Isn't this——

The COURT. Let him read it.

Mr. EPSTEIN. I'm sorry.

The COURT. Don't interfere with him.

The WITNESS. What I am saying is that the Food and Drug Administration would approve this kind of drug for use even though a double dose can easily kill a patient by their bleeding to death, but because it has a known pharmacological effect they assume it must be beneficial for the patient. In actual fact, twenty years have now gone by [264] with use of dicoumeral for the treatment of coronary thrombosis and now we begin to get questions as to whether in fact the patients are living any longer or not. It has a proven effect but is it beneficial? I say duo-C.V.P. is beneficial even though we cannot prove very easily how it works. It is utterly safe and beneficial and maybe the F.D.A. should concern itself with the dangerous drugs.

By Mr. EPSTEIN:

Q. Doctor, when you say that C.V.P. is safe, are you telling me that it is safe because there is no toxic reaction in the patients that you have observed?

A. You can give ten times the dose without any harm. I have never done it, but you could.

Q. I am asking you specifically are you telling me it is safe because you have never observed a toxic reaction in a patient to whom you have administered it?

A. From that point of view it is safe and I think from the other point of view it is equally safe because I rely on the intelligence of the doctor, as he pointed out before, if you have capillary fragility and brain tumor no doctor is going to imagine that by treating the capillary fragility the brain tumor will go away. You have to rely on the intelligence of the doctor to know what he is treating.

Q. Doctor, on that statement, when you say that C.V.P. is safe because it doesn't have a toxic reaction, [265] are you also telling me that it is safe to give—Would your answer be that it is safe to give a patient a drug which you know that there is a drug of better or first choice therapy in a given disease situation?

A. I am glad you brought that up because the question was raised this morning, how do you treat capillary fragility——

Q. No. I want to know what——

The COURT. Let him answer.

Mr. EPSTEIN. All right, sir.

The COURT. You have asked him. Now he is entitled to answer it.

The WITNESS. We had evidence from the hematologist this morning concerning the causes of capillary fragility. Now, when a patient comes in with a bleeding problem what happens is that all the tests that can be done in the lab are ordered and the blood is sent down——

Mr. EPSTEIN. Doctor——

The COURT. Let him finish.

Mr. EPSTEIN. I'm sorry.

The WITNESS. I'm sorry.

The COURT. I think it is fair to let him finish.

The WITNESS. The blood is sent down to the laboratory. The hematologist gets the blood. The blood [266] vessel stays up with the patient and the doctor who has to treat the patient.

Now, the hematologist is an expert in clotting and whether blood will clot or not, and C.V.P. has no function whatsoever in any of these clotting problems in which the hematologists are experts. It is good for the vessel wall. Now ninety-nine out of a hundred patients who have these excessive bleeding problems that I treat, the excessive menstruation, first we have to rule out cancer. Then we have to rule out pregnancy. We have abortion. We have to rule out other kinds of disease and we are left with a group of patients who have capillary fragility and excessive bleeding. I send their blood to the hematologist. Ninety-nine times out of a hundred there is not clotting disorder, but I am left with the patient with capillary fragility. He doesn't get her. He gets the clotting problem. I've got the patient with the excessive menstrual bleeding. And there is no——

The COURT. Doctor, what you are saying——

The WITNESS. What I am coming to at the end there is no alternative treatment except cortisone and cortisone is very, very potent and a very, very dangerous drug. I don't know of an alternative except you can put them on the contraceptive pill. That is one way, and the other way is to treat them with this, which is a very mild beneficial and harmless drug, and——

[267] The COURT. So what you are saying, doctor——

The WITNESS (continuing). So if you had an alternative which was better you could condemn this, but in the absence of an alternative the argument does not hold up.

The COURT. What you are saying, doctor, is that from a hematologist's standpoint it may not have any effect as far as clotting is concerned.

The WITNESS. It does not affect clotting at all.

The COURT. But because it does not have any effect on clotting does not say that it does not have any effect on the other symptoms or causes of this capillary disorder. That is what you are saying?

The WITNESS. Exactly so, sir.

The COURT. That sounds rather logical.

Mr. EPSTEIN. Now, may I ask him my question again, your Honor?

The COURT. Yes. He answered it, I thought.

Mr. EPSTEIN. No. I think what I asked him and what I would still like the answer to this—

The COURT. You want to know if there was a better substitute would it be harmful, and he said first there is no better substitute except cortisone.

Mr. EPSTEIN. I didn't ask him about C.V.P. products. That is where we launched into this discourse.

[268] I had asked him as a physician if there is a drug of better choice, if there is a preferred treatment do you give a lesser treatment, does he consider it safe. That is all I wanted to know. I think it would be a yes or no answer.

Mr. HOFFMAN. Your Honor, the answer——

Mr. EPSTEIN. We have listened to what he said. I just want him to answer my question.

The COURT. Gentlemen.

Mr. HOFFMAN. I objected to the question.

The COURT. Gentlemen. I know it is getting late but let's keep your seats.

I will say he does not have to answer the question. It is theoretical. It doesn't mean anything. It is one of these stop beating your wife questions.

Come on, let's get on with the case. I mean what has that got to do with it? Different people do not all use the same drug for anything, and it would be awfully hard for me to be convinced of that. There is not an absolute certainty in any med-

ical treatment. Most of them use the process of elimination in order to find out what is right to do under a particular circumstance. Isn't that right, doctor?

The WITNESS. Absolutely, sir.

The COURT. There is no absolute certainty and pick out of this bottle and that is a cure for everything.

[269] The WITNESS. No. I think the F.D.A. wishes medicine were a science.

The COURT. Let's get on with it.

By Mr. EPSTEIN:

Q. Doctor, do you treat patients with hemorrhagic duodenal ulcer?

A. No. I treat only women for gynecological and obstetrical conditions.

Q. So that as to the list of diseases or ill states that are described in the Exhibit C——

The COURT. He said he has not read Exhibit C so I will not let you ask him anything about it. He said he hasn't read it. So there's no use for him to go over it. He is not familiar with it so he is not qualified to testify and he said he was not. So you can make the most of it. He said he hasn't read it. Is that right, doctor?

The WITNESS. Yes, sir.

By Mr. EPSTEIN:

Q. So then do I understand then, doctor, the extent of your knowledge and use of C.V.P. products is only then in the case of women who have gynecological or obstetrical problems, you have never been exposed to it other than that?

A. I have read a great deal other than that.

* * * * *

[271]

By Mr. EPSTEIN:

Q. Have you done any other experiments, doctor, any other clinical studies other than the one you have just described to us?

A. Yes, I have done many studies, but it is difficult to control them in the way that that first one was because it is very difficult to treat a patient for long with a placebo. If you start to give a patient sugar instead of [272] genuine treatment they are jolly soon back on your neck complaining that they aren't

getting better and you have to do something to give them genuine treatment and if you are going to give half your patients for three months, as in that study, a placebo, you very soon run into trouble and your colleagues who referred the patients to you start to object, so I haven't been able to continue as a controlled study, but I have continued to treat patients with this treatment with mostly beneficial results, some so beneficial that if this drug were withdrawn from the market I don't know what I would treat them with.

* * * * *

[275] Whereupon,

[Murray Joseph Miller was called as a witness and, having been first duly sworn, was examined and testified as follows:]

(Dr. Miller's curriculum vitae was marked for identification as Plaintiff's Exhibit No. 7.)

The COURT. Let his qualifications be admitted and I will approve him on his qualifications as being an expert and permit him to testify to save time.

The CLERK. Plaintiff No. 7.

Mr. HOFFMAN. Thank you, your Honor.

(Plaintiff's Exhibit No. 7, heretofore marked for identification, was received in evidence.)

DIRECT EXAMINATION

By Mr. HOFFMAN:

Q. Would you state your name, please, for the record, doctor?

A. Murray J. Miller.

Q. And what is your present position?

A. I am chief of medicine and chief of staff at Quakertown Community Hospital and instructor in medicine at Hahnemann Medical College and Hospital.

Q. Are you acquainted with C.V.P. and duo-C.V.P.?

A. I am.

Q. Could you tell us the circumstances in which you [276] became acquainted with them?

A. I was assigned to the Naval Hospital in Annapolis, 1957 to 1959, as assistant chief of medicine. As one of my volunteer duties I was functioning as a coach and medical physician for the 150-pound football team, as a medical consultant to the wrestling team. We were troubled with quite a few soft tissue injuries from the contact sports and accordingly searched the literature to see if there was some medication that might be

of value in decreasing either the frequency or the severity of the soft tissue injuries.

Q. Have you used C.V.P. in your practice?

A. I have.

Q. Do you now?

A. I do.

Q. Has any of the research or studies that you were describing a moment ago with the C.V.P. products ever been published?

A. Yes, it has.

Q. Where?

A. I believe it was in 1960 in the Medical Times on the experimental work I did while at the Naval Academy.

Q. Doctor, in the course of your work with C.V.P. and your studies of the product, have you had occasion to become familiar with the scientific literature as to those products?

[277] A. A good bit of it.

Q. Have you discussed the C.V.P. products with other experts?

A. Yes.

Q. Have you ever heard or read of any adverse reports on the safety of C.V.P.?

A. None whatsoever.

Q. With respect to any condition of use?

A. None whatsoever to my knowledge.

Q. Do you have an opinion whether or not on October 9, 1962, qualified experts generally recognized that C.V.P. and duo-C.V.P. were safe for use in treating abnormal capillary permeability and fragility?

A. It was considered safe.

Q. Generally considered safe by qualified experts?

A. Yes, sir.

Q. Do you have the same opinion as to the state of expert opinion today?

A. Yes, I do.

Q. Did you hear the testimony of Dr. Spaet this morning?

A. Yes, I did.

Q. And of Dr. Corn this afternoon?

A. Yes I did.

Q. Do you recall what specialty they indicated they [278] practiced in?

A. They are hematologists.

Q. Do you recall hearing the list of underlying disease states that counsel for the defendants, Mr. Epstein, read part of to Drs. Karpman and Clemetson this afternoon?

A. Yes, I did.

Q. Is it your opinion that a hematologist would, if he had a medical practice, treat patients with those conditions?

A. To the best of my knowledge, hematologists' patients are usually referred to them by other physicians for problems of bleeding or blood components rather than the organs that they contain.

Q. I am not clear on the answer to the question.

The COURT. He made it clear to me.

Mr. HOFFMAN. Okay.

The COURT. He said their problems in the main were limited to questions of blood and blood quality and treatment.

The WITNESS. Yes, sir.

The COURT. They are specialists in blood itself and the actual product; isn't that right?

The WITNESS. Yes, sir, and the blood-forming organs.

* * * * *

[309] * * *

Mr. HOFFMAN. Your Honor, respectfully, we do not think you determine the safety of the drug at all. We think what you have to determine is whether there was in 1962 a concensus of expert opinion that the product was safe, and we think the testimony of these witnesses, all five of them, shows that the concensus was, in fact, that the product was safe. The Defendants' witnesses said, "Ah, but there wasn't a concensus that the product was effective," and they went further than that, but that is as far as the Government had to go in this case, and because these two doctors said there was not a concensus that the product was effective there could not be a concensus that it was safe.

We do not think the Court has to determine, your Honor, whether the product was, in fact, safe. We do not even think the Court has to determine whether—I am sorry—we do not think the Court has to determine whether the product was, in fact, safe or, in fact, effective, and we do not even think the Court has to determine whether there was a concensus that the product was effective because we have made clear our position all along in this case that while we think the product is

effective we recognize that there was no concensus in favor of that effectiveness.

What there was a concensus in favor of, your Honor, was that the products were safe. * * *

* * * * * *

[314] * * *

Well, your Honor, as with the zerex analogy we believe that this is false reasoning. We think it is an attempt to put something in the statute which is not there and for one thing, your Honor, as a question of statutory interpretation, it overlooks the fact that in 1962, when Congress wanted to add the concept of effectiveness, efficacy of the drug to the statute, it took an enormous legislative battle to do it, the Kefauver-Harris Amendment of 1962, following the thalidomide events.

So, for the Government now to say that the word "safety" which has been in the statute since 1938, all along meant that incorporated concepts of effectiveness, we think just misses the whole point.

Now, Dr. Spaet testified in his view that the product was not safe because it did not work, but he said it did not cause any harm by itself, that he never heard of any harm by itself, and the only basis on which he could say, the only basis on which he could give the conclusory testimony that in his view experts didn't think the product was safe was by relating it to this concept of efficacy.

[315] Dr. Corn, if your Honor will recall, if he ever got to give this testimony, and I am not entirely certain whether Mr. Epstein ever actually got him to say, was apparently prepared to say something like this.

The COURT. He said the same thing. I mean I cut him off somewhat and said clearly, Dr. Corn would have said, had he been allowed to ask, and I accepted it as such, that he would reach the safety factor by identically the same method that Dr. Spaet arrived at. In fact, I clarified that myself and said his opinion would be the same. So the mere fact that the Court, to save time, did not allow Mr. Epstein to go over each of the same questions, I will accept his testimony as duplicating, corroborating exactly what Spaet said.

Mr. HOFFMAN. Respectfully, your Honor, for the record, we would not so stipulate, but I understood the Court's ruling and I will move on.

Now, the question then is: What was the consensus? We think as a legal matter the concensus of expert opinion in 1962 was that the product was safe because of the legal deficiencies in this efficacy equal safety theory propounded by those two doctors, but beyond that, your Honor, the Government is probably going to tell you in their argument that whenever you have a conflict of opinion as to what the concensus is, that is one expert has gone around and taken a [316] concensus and he says one thing and another expert has gone around and taken another thing, the Government will tell you that that conflict means that there is no concensus, and they are going to cite to the Court, your Honor, two district court decisions of some vintage that seems to say something like that.

Respectfully, your Honor, we think that is simply not the law. * * *

[320] Mr. HOFFMAN. That, your Honor, we would submit is Mr. Epstein's problem, but more importantly Dr. Spaet and Dr. Corn each did, in fact, go down both paths. We think they both said that, well, the product was generally recognized as nontoxic, so that to the extent that that is the governing premise and the one on which Drs. Karpman, Clemetson and Miller testified, Dr. Spaet also went down that path, and he did not disagree.

Your Honor, moving, if I may, briefly, from this point, because we think that this evidence does show that, No. 1, the expert concensus in 1962 was that the product was safe. We think all the doctors except possibly Dr. Corn, who may not have gotten to that, did say that, and he did not say anything to the contrary.

We think that under the relevant statutory meaning of the word safe the product was, therefore, generally recognized as safe, and we also think, of course, that the weight of the evidence is that even among doctors the word safe does not have that highly forced and far-fetched meaning that Dr. Spaet and Dr. Corn tried to give it.

We think that we have to go on and show that the other two prerequisites, so to speak, to the application of the grandfather clause were met, and we do not think there is any real dispute about one of them. The first, or I should [321] say the second prerequisite of the grandfather clause is whether a product was in commercial use and sale on October 9, 1962.

The COURT. Well, they do not dispute that.

Mr. HOFFMAN. There is no dispute about that.

The COURT. They do not dispute that. It was clearly in use at that time.

Mr. HOFFMAN. We will move past that, your Honor.

The other point has to do with whether the product was covered by an effective new drug application at that time because the statute, the grandfather clause says you are exempt from this new area of regulatory authority given to the commissioner in 1962 if, first, you were in commercial use in '62, which we are; second, if you were not a new drug on October 9, 1962, under the statute as it then stood, and this is the subject that your Honor and I have just been discussing; and, third, if on October 9, 1962, the product was not covered by an effective new drug application.

Now, this later point is a matter of no factual dispute and enormous legal dispute, and, of course, nothing whatever was said about this on Friday because it is not an evidenciary matter. The facts there is no disagreement on. The facts are that in 1955–56 some but not all of these products were the subject of new drug applications, which were [322] filed with the Food and Drug Administration and allowed to become effective. The fact, further, your Honor, we think as based on the evidence that we have just been discussing is that sometime thereafter the products ceased to be new drugs; they became through use, through use over a material time and to a material extent——

The COURT. You mean subsequent to '55.

Mr. HOFFMAN. Subsequent to '55, your Honor, they became through this material time, material use generally recognized as safe and no longer new drugs, again the point we have just been discussing.

And so, your Honor, the Food and Drug Administration actually recognized in a series of letters which were put into the record by stipulation and the relevance of that I think, without meaning to belabor the point, because it did come up very briefly on Friday, is that the Food and Drug Administration is the official agency which is responsible for administering the Food and Drug Act, and while they do not conduct proceedings to determine it, they do have some expertise in deciding whether a product is a new drug or not a new drug.

That is what Dr. Smith's business was. He is the man who wrote those letters, or most of them, and he said the products were no longer new drugs.

* * * * *

[326] * * *

Mr. HOFFMAN. Because all I am saying is that this bioflavonoid, this citrus flavonoid compound which is in the C.V.P. products having been on the market before and being an old drug can continue to be marketed and to the extent that it is put up in a new package or something like that if the claims are the same and the ingredient is the same this product is not a new drug. It does not make it a new product just because you might put a new package on it, if the claims are the same. It does not make it a new drug—well, it might be a new drug if you added something to it, but then the bioflavonoid part of it would not be a new drug.

The COURT. If you mix it with something else doesn't it become new?

Mr. HOFFMAN. To the extent that something new was added it would be new and that is all, and that is what Dr. Smith recognized in 1961, your Honor, in those letters when he said that to the extent that the citrus bioflavonoid compound is involved this is not a new drug. So he was recognizing, as he had previously, that through general use over a period of time the citrus flavonoid compound products [327] manufactured by Plaintiff were not new drugs.

Now, it is our position that as a matter of law, and we are just relying on these FDA letters by way of dramatizing the position, to the effect that they agreed with us then. We say that as a matter of law, the products then were no longer covered by an effective new drug application and the Government says, well, yes, they were because once covered always covered; you filed it and therefore you were covered.

Now, your Honor, respectfully, there is absolutely nothing to support that once covered always covered approach except what Government counsel says. There is nothing. There is no legislative history. There are no cases. There is nothing in the statute. They just say it as if it were a verity.

But I think we have to look a little beyond that and see what happens to a product when it is covered by an effective new drug application. Even then in 1962 certain things needed to be done. There was an on-going system of administrative controls.

Now, it is our position, your Honor, that once a product became no longer new and the agency's own regulations at the time recognized that such a thing could happen, the product

ceased to be covered by an effective new drug application. The company could when it concluded that the [328] product was no longer new have withdrawn its new drug application. It could, so to speak, have gone down and asked for its copy back or if that was not precise procedure effected a withdrawal so that the thing was no longer carried on the books; but that is a matter of form, your Honor, and we think——

The COURT. If they did not withdraw it what happens?

Mr. HOFFMAN. We think that the product still was no longer covered by an effective new drug application because unless the phrase is just a meaningless repetition of abstractions, it has to have some content. The only content can be, first, does the product need that effective new drug application to be marketed and, second, is it subject to the on-going administrative controls of FDA, and the answer is in this case, even though the piece of paper remained in the files, neither of those things were true, so that the product as a practical matter was no longer covered by an effective new drug application on October 9, 1962.

* * * * *

[331] * * *

So we have this system of on-going administrative controls which we think represents the real meaning of the phrase covered by an effective NDA, and we think further that our products were not covered by an effective NDA on [332] October 9, 1962, because the products having ceased to be new were no longer subject to that system; they were just as if the products had never been NDAed. They were just as if the product from the moment of its conception had been generally recognized as safe.

The COURT. If I understand you correct, and I will accept this unless the Government corrects it, corrects you or questions you, do I understand that a new drug applications prior to 1962 automatically became inoperable by statute after the passing of time unless there was some ruling or contrary evidence promulgated by the Food and Drug Administration. In other words, if I filed a new drug application strictly in accordance with law in 1950, and I consistently marketed the drug up until 1962, strictly in accordance with statutory requirements, I am talking about this old drug that I got the application—now, by statute, I understand you to say it automatically become old because over this period of time—I mean assuming

it had been factually accepted in the market and constantly used, that it automatically became an old drug and, therefore, did not come under this present Act.

Mr. HOFFMAN. Well, automatically may have connotations that may be confused.

The COURT. It has to become old—what I am getting at and I want you to get your position, it either [333] becomes old by the passing of time and use——

Mr. HOFFMAN .That is right, your Honor.

The COURT (continuing). Or it becomes old by operation of statute.

Mr. HOFFMAN. The statute did not say anything about it. In effect, the new drug application became obsolete, because in the passage of time the drug became old, it no longer needed the application to be marketed and the application just became superfluous through the passage of time. That is the essence of our position.

The COURT. All right.

* * * * *

[350] * * *

The COURT. I only read, too, Mr. Epstein, but, unfortunately, everybody does not read the same. I mean we look at the print, but we do not come up with the same impression. Now, read the whole thing. What does it say? I mean you have to read it all. You cannot read things out of context.

Mr. EPSTEIN. I read it——

The COURT. Look at any of those exhibits, and, clearly, what does it say? It has a great big triple headline on the front page, and you would clearly have to read that the tonsillectomy it referred to was not the cutting out of the tonsils—that is a tonsillectomy—it was not designed to stop bleeding, the obvious bleeding, that flows from the cutting out—a tonsillectomy. I do not know how you can read it to say that it did not refer to capillary fragility, and so forth, resulting therefrom. Now, is that not what it says?

Mr. EPSTEIN. No, it does not.

The COURT. Why doesn't it say it?

Mr. EPSTEIN. Well, because, in the labeling, Your Honor——

The COURT. I am talking about that page.

Mr. EPSTEIN. The same piece of labeling, and Dr. Spaet testified on that specific point, the representation was [351] made, "Clinically, the anti-hemorrhagic effect of C.V.P. products——"

The COURT. Dr. Spaet did not intrigue me too much on that testimony. All he said was, clearly, he could read that and it would not cause him to be taken in.

Mr. EPSTEIN. But the issue, Your Honor——

The COURT. Wait a minute. All he said was it would cause the average doctor in Northern Virginia to be taken in because the average doctor is not as smart as he is. I do not buy that argument, with all due respect to the doctor. He says he is a hematologist and "that would not take me in; it would not fool me at all, but the general practitioner that does all the work, that uses all these pills in Northern Virginia or in Northern New York"—he put both—"they would be taken in. They would buy this in the full expectation that it would stop an operational, post-operation, bleeding." I would say, if he got taken in that much, he ought to lose his license. It does not read that way to a layman. I just will not read it that way.

Mr. EPSTEIN. Well, Your Honor, the labeling for these products is directed to doctors. The layman never sees the labeling.

The COURT. I know, but it would not take me in as a layman. It certainly ought not to take a doctor in, should it?

* * * * *

[395] * * *

[Mr. HOFFMAN]

It is true that for a year or two, or thereabouts, we submitted changes in the labeling to the Food and Drug Administration as required when a product is still a new drug. Thereafter, we did not and, in fact, the correspondence between FDA and our company which is in the record and about which there was some discussion, was correspondence that really was concerned with that question, whether we had to or [396] not, and the thrust of those letters being that the citrus flavonoid C.V.P. element was no longer a new drug, we stopped submitting new labeling, we stopped submitting changes in the method of manufacture because we were no longer a new drug and, in fact, the Government has made that absolutely crystal clear in its admissions which are on file in this case because if your Honor will remember from Friday they said they did not have all the labeling that they could say was being used on October 9, 1962, that was not in the files. Why wasn't it in the files? Because we did not submit it.

Now, Food and Drug Administration regulations in force in 1962 contemplated precisely this situation.

The COURT. Wait a minute, so I will get it. You say that the record and the admissions here show that you have effectively withdrawn your new drug application previously introduced.

Mr. HOFFMAN. In practical effect it is if we had.

The COURT. I say effectively withdrawn as shown by your correspondence with the agency clearly indicating that you are not going to send any more because it is not a new drug.

Mr. HOFFMAN. That was the substance of it.

The COURT. And you are going to take your chances on seizure and let them seize be damn because it is an [397] old drug and once they seize and there is no new application you will defend the seizure; is that what you are saying?

Mr. HOFFMAN. Well, it was not in that posture of defiance, your Honor.

The COURT. I know you are not complaining—you are not encouraging a seizure but that is the net effect of it.

Mr. HOFFMAN. Well, it would be except in effect we had the agreement of Food and Drug Administration. The record includes the letter that we wrote in 1961 referring to the previous letters commenting that it would appear that this means that the agency no longer regards the products as new drugs.

* * * * *

[418] The COURT. I did not take any evidence this morning.

Mr. HOFFMAN. Your Honor, I understand that.

Your Honor, this was never an issue in the case until it just came up at the close of the morning recess. We relied on their admissions in the answer, on the statements in their statement of material facts.

The COURT. That you had withdrawn?

Mr. HOFFMAN. Sir?

The COURT. That this application had been withdrawn?

Mr. HOFFMAN. No, not the legal conclusion that it had been withdrawn, and certainly not that a formal withdrawal document, something that looks like a will and testament had been filed.

The COURT. Do you say that there has never been an issue in here whether or not this application has been withdrawn?

Mr. HOFFMAN. We say it has never been an issue in here that for some years——

The COURT. Has it been conceded it has been withdrawn?

Mr. HOFFMAN. Your Honor, we are not contending it was withdrawn formally. We have always contended——

The COURT. I understand that. All I want to [419] get and really I just want to know what the record shows. You say that you now are—come under 107(4)——

Mr. HOFFMAN. Right, Your Honor.

The COURT (continuing). The parent grandfather—because you didn't have a NDA application pending because it had been withdrawn and they admit it has been withdrawn.

Mr. HOFFMAN. As your Honor said effectively withdrawn, practically speaking.

The COURT. That is right.

This is all the evidence you have in support of that?

Mr. HOFFMAN. This is the evidence and we have the documents here which are referred to in this paragraph of the complaint.

The COURT. Just pass them up.

Mr. HOFFMAN. All right.

The COURT. That is all I want is your evidence. I don't want him to stipulate anything.

Mr. HOFFMAN. There are three letters, one of which is in the record already as Exhibit C to the stipulation, and these are the other two.

The COURT. All right.

Mr. HOFFMAN. The sequence was a letter of February 28, 1961——

The COURT. All right. I just got this letter?

[420] Mr. HOFFMAN. Right, your Honor, February 28, 1961. It is a 2-pager. Then the letter responding to that is the letter——

The COURT. I don't have that. This is just asking them. Where is the letter?

Mr. HOFFMAN. The letter they wrote back is Exhibit C to the stipulation, your Honor. That was put in on Friday, and that is the letter of April, something, 1961, where the Commissioner said as to two of the products we don't regard them as new drugs, and as to the others we don't have the current labeling before us, and, of course, they didn't have it because it hadn't been submitted because the company no longer regarded the product as a new drug.

So he said I will agree or disagree with your position——

The COURT. Look. I don't want you to argue. I just want you to hand me the information. I am going to look at it myself——

Mr. HOFFMAN. Okay, your Honor.

The COURT. I am looking at what you have.

Mr. HOFFMAN. This was——

The COURT. Give me C.

Mr. HOFFMAN. Exhibit C.

The COURT. Is this all you have?

Mr. HOFFMAN. No, your Honor. Then there is [421] the third letter.

The COURT. Exhibit C.

Mr. EPSTEIN. Do you want this back?

Mr. HOFFMAN. No. That is your copy. You may have it.

Mr. SMONSKEY. I know where it is in the file.

Mr. HOFFMAN. Perhaps Mr. Smonskey can help us on that.

Mr. SMONSKEY. Exhibit C is right in there.

The COURT. That is all I want.

Mr. HOFFMAN. Exhibit C, your Honor.

The COURT. All right.

Mr. HOFFMAN. And then the third letter responding to Exhibit C.

The COURT. All right. Just give it to me.

Mr. HOFFMAN. I believe that was handed up, your Honor. There were two letters that I just handed up.

The COURT. That is right, two attached to it. They are both requests for the status. That is all those letters are.

Mr. HOFFMAN. No, your Honor. May 16, 1961, says, "This is in reference to your letter responding," and it says, "It is our recollection that the C.V.P. class of products," and this is the third paragraph, "were no longer considered to be new drugs the short time after the NDA became [422] effective." That was the statement of position.

The COURT. I understand that is what you say, but that isn't what they say.

Mr. HOFFMAN. They didn't respond.

The COURT. I see.

Mr. HOFFMAN. They didn't take a position.

Finally, your Honor, we have copies of a letter that was submitted to the Food and Drug Administration in 1965, in which the company—this was with regard to a collateral discussion——

The COURT. All right.

Mr. HOFFMAN (continuing). As to whether or not certain newly imposed reporting requirements that the Commissioner said were applicable to new drugs were applicable to these

products, and a sort of a semi-response was made to that request to comply with the reporting requirements with the final paragraph, "This information is being submitted with prejudice to our position that you do not have the legal authority to acquire reports with respect to drugs which are no longer new drugs and the submission of the above information——

The COURT. All right. You do not need to read it to me. I will read it.

Mr. HOFFMAN (continuing). Does not constitute an implied information."

[423]

(Correspondence between HEW and USV Pharmaceutical was marked for identification and received in evidence as Plaintiff's Exhibit No. 8.)

The COURT. Do you have any other evidence? This is all you have?

Mr. HOFFMAN. The last fact I point to your Honor is that as conceded and stipulated in this case, in fact asserted in the answer, two of the products were never covered by an NDA by anyone's definition because no NDA was never even submitted for them. Those are the——

The COURT. They still reserve the right to do it. They say it is open in perpetuity.

Mr. HOFFMAN. They may say that we were entitled to it, but we never did. So we think what this demonstrates, your Honor——

The COURT. I don't want you to argue it. We will get that later. I don't want you to demonstrate anything. I have heard it.

Mr. HOFFMAN. Okay, your Honor.

The COURT. All right.

* * * * *

[441] * * *

Mr. HOFFMAN. I would be delighted to close the presentation of the case and the plaintiff's argument and hopefully submit the case. There are only three simple points that I would like to make in response to Mr. Epstein.

One is that regrettably he is again wrong on the law when he says an applicant cannot come in and pull out his new-drug application because Section 130.8 of Title 21 of the Code of Federal Regulations says, and this has been in effect in substantially the same form for years and years, long before 1962, "The applicant may at any time withdraw his pending applica-

tion from consideration as a new-drug application upon written notification to FDA."

The COURT. I understand that.

Mr. HOFFMAN. All right.

The COURT. As I said, I don't even need a Federal regulation. He obviously can.

Mr. HOFFMAN. Okay. The next——

The COURT. But that doesn't help you much because you didn't give them that written application.

Mr. HOFFMAN. We did not give them the notice [442] in the language of the regulations. What we did do is write to them and say we think these products are no longer new drugs. Do you agree? And they said, Gee, we don't know. You haven't been sending in the labeling.

The COURT. Let me get you right down to the nub of this case. Are you willing to stipulate now and for the record, thereby estopping yourself from taking a different or an untenable position—I am not trying to box you, now, so be careful, in a corner that you can't get out of—that it was always, eventhough they did it a little clumsy and didn't have good expertise in the legal field and write the letter, you know, and crossing all the Ts, and so forth, as this section expressly provided; but that is what you intended to do all the time from way back 1962—'51—I mean——

Mr. HOFFMAN. From '57, your Honor.

The COURT (continuing). From there, yes, '57, that is what you intended to do all the time; you didn't write the letter because you did write to the government and you understood and relied on it that they accepted what you had done as a letter, at least that you thought that, so it was always your intention to withdraw this new-drug application and take whatever chances the law exposed you to for marketing it unapproved, and if you stand on that position now I am liable to accept you at it and then there won't be any question about them seizing you if they want to.

* * * * *

[444] * * *

The COURT. And you intended to withdraw your application. Now, I don't want any equivocation.

Mr. HOFFMAN. Your Honor, the statute uses the phrase——

The COURT. I don't want you to here argue with me any further. If you are telling me now that you didn't have the inten-

tion to do what you want me to read all of this stuff to draw the conclusion that you had an intention, I am liable to agree with you. Now, if you did have the intention I am inclined to agree with you. I like to help you do what you wanted to do.

Mr. HOFFMAN. Your Honor, I have to say that obviously the company, the company's business people and scientific people weren't thinking in the statutory terms, and I know that I certainly and our firm certainly was not involved with the company at that time, so I cannot say what was in their heads. I can say, and I can stipulate to this, that they intended by this correspondence and by continually asserting the position that these products were no longer new drugs that they no longer required an NDA in effect to be marketed and that——

The COURT. And they acted accordingly.

Mr. HOFFMAN. And they acted accordingly.

The COURT. From that date on they have treated [445] these as drugs to be marketed without a NDA approval?

Mr. HOFFMAN. That is exactly right, your Honor.

The COURT. All right.

Mr. HOFFMAN. Now, the only thing left, as I see it, is the Quinaglute case, which is I believe cited through the briefs that were—at least in our briefs filed a year ago. As Mrs. Sisk put it in the tail-end of her quotation or summary of the Senate Committee report, the question, even on taking them at their face value, is whether the product was effective for a life-threatening condition, and as your Honor has I hope made clear, I believe it is clear to us, the label used for this product was, is and has been abnormal capillary fragility and permeability. There is no suggestion in the record that that is a life-threatening disease regardless of whether the more serious disease states which accompany it may be, but those were not what the products were recommended for.

So, we say, your Honor, that Quinaglute has no application here. That is not authority for the position that the government asserts. The action of Congress in importing the concept of efficacy into the statute after a furious legislative battle in 1962 should be dispositive as to what the statute before that——

The COURT. Why do I get to that? Again I don't have to get to that in this case. You either come under the grandfather clause or you don't.

[446] Mr. HOFFMAN. We agree with that, your Honor.

The COURT. All right.

Mr. HOFFMAN (continuing). And we think we have proven all the elements.

* * * * * *

[448] * * *

By The COURT:

I also find without any difficulty that the question here—I think this statute is devisable. I think it does apply as both the government has aptly said and Mr. Hoffman has indicated that if it is a new-drug applicant, if it is a matter that is before the Food and Drug Act by virtue of a previously filed new-drug application approval form and is a continuing matter before the bureau by virtue of the continuing duties of notification, relabeling, remanufacturing, and the other prerequisites, I think it is the kind of a new-drug application that gives the Administrator under Section (b)(3) clause, as I will call it—3(b)(3) I guess you have characterized it, to have this two years, you know, hiatus, it will stand approved as of that date, and during this two-year period they can't do anything about it, and I think it is directly for the purpose of giving the manufacturer the opportunity to gather such data as he might need to have if he is called upon to submit any additional information in reference to both the old requirement, which was safety, and the new requirement or the new-coupled requirement of safety and efficacy.

[449] I think the 107(4) as I will call it, that is the final paragraph, is clearly a catchall which says in any case—in other words, if it is an old drug, one not pending, it just doesn't come before it and it is up to the government to do what they want to if they think that old drug doesn't meet minimal governmental standards for safety or efficacy. I think they have to get at it by seizure—I mean which is the basic way the government gets at it.

So, therefore, I now find myself in that unique position as to which category you fall in.

There is evidence here, and the government has admitted certain parts of it on admitting the so-called paragraph 9. The plaintiff augments that by some letters and so forth from various government officials, Dr. Smith particularly, certainly pertaining to his dealings with the bureau in connection with this matter; that is, he is inquiring whether they are considered old or new.

I have to assume, and I don't think it is a violent assumption, that a company of this size and type would have general knowledge of pending legislation, you know, effecting their product, and I would have to assume that the drug company knew that they were broadening the safety requirement by the amendment by including the word efficacy, or at least the government hoped to, and that it would probably apply from then on, because this would be '61, just before and [450] that is when some of this was going on, '60 and '61, just before the adoption of the Act in question or the effective date, and, of course, this hearing was going on before.

The company appeared to take the position that they were in the old drug. They say, and there is nothing to contradict them, that this record appears to show from then on they didn't change their label. If they did they didn't let the government know anything about it, and they didn't tell them anything more about it; and, as a matter of fact, they didn't do anything about it.

Now, they were trying to keep on both sides of everybody which isn't an unusual phenomenon, because when the bureau went into this new situation under the NAS investigation, under the paragraph 3, assuming it was an old—I mean an approved drug on the form and asked for additional data to support the safety and efficacy of the drugs in question, they did comply by giving—furnishing information—I mean I think that is clear, they did it, but I don't know that that makes it inconsistent, and it would have made it inconsistent, been fatal to that company had they not frankly stated in writing they were submitting this without prejudice, see, to their then and long standing claim that they weren't covered by that new-drug application because it just—they were not a new drug; but, nevertheless, they were going to give you this information in the hopes that we would stave off any [451] seizure or approval or whatever you might had in mind. Well, you can't hate them for doing that.

Now, we get back to the other question. You say this safety question—I am not interested in determining that other than using the—I mean this doctor's testimony that we had under the old-drug formula, as I call it, really is of little value to me other than it is testimony as to whether this drug was in fact a new or old drug in 1962—I am talking about factually, and notwithstanding the pendency of a drug application.

I would be of the opinion that even if it were an old drug, technically speaking, due to age and safe propensities, if there was a pending application, you know, approval form as a new drug that they had to go along, it hadn't been for any purpose withdrawn, it would still come under Section 3, because I think the only ones that are excluded in this last one are those who either didn't have an application or if they had a new-drug application it had been effectively and for all practical purposes withdrawn.

The definition of "safe" says it must have some effect. I think the exact word is reliance on the health. 268—I don't remember, but let's look at it. I think that is what it says—the statutory definition which is not always—it says, "The term 'safe' as used has reference to the health of a man."

[452] Well, if it is innocuous, if it is so nebulous that it is not good for anything as the government contended, and that is all the evidence they had, see—I mean all the government said it just was a harmless piece of some kind of juices extracted or chemicals extracted from citrus fruit coverings that might as well give them tap water; it just didn't mean anything.

Of course, other doctors disagreed with that, and even if they were correct that wouldn't take it out of the word of safe—I mean make it unsafe.

Thirdly and lastly, including the counsel's open admission and strong affirmance, I will assure you he can't back out of it if he comes to this Court; he will have an awful time backing out of it or anybody else, that it was always their intention if they did not fully and completely comply with the administrative requirement of writing an actual, technical, formal letter, saying, "I withdraw Application No. 32, per se," and sign it. All the action and plus the intention of that is what they intended to do, and that is how they reacted for eight years, I would be inclined to find that they had effectively withdrawn it and this comes under Section 4 and that they are exempt under Section 4 on this record as being a Class 4 job and with the expressed understanding that it is understood by all concerned that if there is the slightest doubt in the Food and Drug Act that [453] there is any harmful effects or any statutory reason why these drugs shouldn't be on the market they should seize them. If they seize them in this jurisdiction I can assure the government that they will get a full and fair hearing and determine whether or not it was a lawful seizure, and that is that. We will dispose of it accordingly.

I also am of the opinion since the Court has held that and at the urgence of the plaintiff, and I agree with him, that he is not what I will call a 3(b) party—of course, the ruling that the commission has made in reference to its Federal Register, you know, as far as I am concerned I am not passing on the validity of that ruling; it stands as far as I am concerned. He can do what he wants to if it is void. They can proceed to enforce it. He can neglect it. In other words, I am just not passing on it. I mean I am making it clear. In other words, the government is free to stand on their Federal Register support if they want to do it because he says he doesn't come within that section and I agree with him, and he's got to come within one, so he wants to come in the grandfather clause as an old drug, and I agree with him.

I will enter an order accordingly, and if either side wants it, they can't work this out, I will write more formal findings as soon as I can get to it. With my docket it may take me a week or two. If they want to accept, you know, my findings, just what oral ramblings that I have made, which [454] are not as definitive as it would be if I, you know, made specific findings and conclusions which I will.

I think I have clarified my situation.

Yes, sir?

Mr. HOFFMAN. Your Honor, may we submit proposed findings and conclusions?

The COURT. Yes, you may do that on this record, I say if you want more; and so can they. You can submit it to them, and the ones that they do not agree with the findings, I will do it accordingly. But so that you understand it they must be in accord with the general subject that I have just said here——

Mr. HOFFMAN. Very well.

The COURT (continuing). And that is to support that you are an old drug and that the old drug is based upon the fact that your application was always your intent to withdraw that and your affirmative acts effectively withdrew it before the effective date of this Act. I mean that is the basis of my putting you in the other category.

* * * * *

EXCERPTS FROM TRANSCRIPT OF PROCEEDINGS IN DISTRICT COURT ON MAY 4, 1971

[12] * * *

Mr. HOFFMAN. Your Honor, the record showed that con-

struing the word "safe" to mean the illogical meaning that the court just described——

The COURT. So that we will get the record clear, I've got many things to do, and this isn't one of them—on page 4 you have asked me to confirm that I found No. 2 that were and are today generally recognized as safe for their intended uses as the word "safe" was then understood. I believe that I said that when I said that the court finds that these bioflavonoids were safe as that word was then understood.

Mr. HOFFMAN. That is fine.

The COURT. I don't know how I can say it any better.

[13] Mr. HOFFMAN. That is fine with us, your Honor.

The COURT. So whether you——

Mr. HOFFMAN. That disposes of No. 2.

The COURT. If that isn't what I said let them tell me what I said.

Mr. HOFFMAN. Fine, your Honor.

As to No. 1,——

The COURT. Now, as your No. 1, you asked me that they are exempt from the new-drug provisions of the statute.

Mr. HOFFMAN. That is correct, your Honor.

The COURT. Well, I couldn't have found that any better in your ways when I made it very clear that that is all I was doing.

Mr. HOFFMAN. That is right, your Honor.

The COURT. I held that this decision, the last paragraph is limited solely to the determination of whether the plaintiff's drugs are entitled to the exemption set forth in the statute; isn't that right? And I held that they were.

Mr. HOFFMAN. That is right, your Honor.

The COURT. Now, I limited it to the exemption.

Mr. HOFFMAN. The only thing we weren't clear on that, your Honor—well, we think we know what the court meant. Technically speaking, the exemption in Section 107(c)(4) is an exemption from the changes in the definition. Now, we are confident that the court intended to hold that the [14] products are exempt from new-drug regulation because of the consequences of their being exempt from the definition, and that was all we had in mind on our point 1 in which we asked the court to confirm that the products are today not new drugs under that old pre-1962 definition and, therefore, are exempt from the new-drug provisions of the statute.

If I understood the court a moment ago correctly, the court said, yes, that was what the court did hold, and that is the confirmation that we are seeking.

The COURT. The court clearly intended to hold that they were exempted by the grandfather clause. Now, that is all period.

Mr. HOFFMAN. Exempted by the grandfather clause from new-drug regulation.

The COURT. That is correct, and that is all I held.

They are not exempt—the government, if they think they are toxic, if the government thinks they are harmful, as I made it very clear in there——

Mr. HOFFMAN. We understand that, your Honor.

The COURT (continuing). The government can seize your drugs tomorrow and take them off the market—I mean under the pure Food and Drug Act. And I only held that they can't require you to go through all this rigmarole because the grandfather clause exempted them. * * *

In the United States District Court for the Eastern District of Virginia

(Civil Action No. 4915–A)

USV PHARMACEUTICAL CORPORATION, PLAINTIFF

v.

ELLIOT L. RICHARDSON, ETC. ET AL., DEFENDANTS

ORDER AND MEMORANDUM OPINION

This Court is of the opinion that the plaintiff's bioflavonoids here in question are exempted from the provisions of §201(p) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301, et seq., as amended by P.L. 87–781, so long as such products are intended solely for use under conditions prescribed, recommended or suggested in the labeling thereof, as of October 9, 1962, and

It Is So Ordered.

The controversy here turns on whether the plaintiff's bioflavonoids are "new drugs," within the meaning of 21 U.S.C. § 321(p), and thus subject to the efficacy review provisions of the amendment of 1902, or whether they are "old drugs" by reason of the "grandfather clause" in the 1962 amendment—§ 107(c)(4).

The Federal Drug Administration has determined that the plaintiff's bioflavonoids are "new drugs" and has called upon the manufacturer to document and establish their efficacy, as provided for in the 1962 amendment.

Rather than comply, or run the risk of criminal prosecution for non-compliance, the plaintiff brought this suit seeking pre-enforcement relief under 5 U.S.C. § 701–704 (Administrative Procedure Act) and 28 U.S.C. § 2201 (Declaratory Judgment Act). That such is proper to resolve conflicts of this type, see Gardner v. Toilet Goods Association, 387 U.S. 167 (1966).

The "grandfather clause," 107(c)(4) of the Act, reads as follows:

> In the case of any drug which, on the day immediately preceding the enactment date [October 9, 1962], (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

If a statute grants exemptions to certain classes of products from its operation and a dispute arises as to whether or not a given product is entitled to such exemption, it is the Court's function—not the Administrator's—to determine whether or not such product is exempted. Thus, this Court has jurisdiction under the statutes above mentioned to hear and determine this controversy between the parties.

The Court's findings and conclusions follow.

The plaintiff has manufactured and sold its citrus line of bioflavonoid products in interstate commerce in substantial quantities from about 1955 to the present date.

Two of the plaintiff's products were never covered by effective new drug applications. The other seven were all covered at one time. These applications, however, were withdrawn prior to October of 1962. The plaintiff made that clear through its correspondence with the Federal Drug Administration. It then ceased compliance with the submittal of data and new labeling, as required by the Federal Drug Administration for products covered by effective NDAs.—The record further discloses that the Federal Drug Administration advised the plaintiff in writing that its products covered by NDAs 11474 and 11475 were not new drugs—and it was stipulated that the compound in these two products is identical to the bioflavonoid com-

pound in plaintiff's other products and that the recommended uses of all the CVP products are essentially the same.

From this evidence, the Court finds that none of the plaintiff's bioflavonoid products in question were covered by an effective NDA as of October 9, 1962.

Whether the plaintiff's bioflavonoids are "new drugs" within the meaning of § 201(p) of the basic Act (codified as 21 U.S.C. § 321(p)) is the key question for determination here.

> "The term 'new drug' means—
>
> (1) Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof. . . ."

The word "safe" as used in the basic Act refers to the health of man or animal [1]—efficacy was not added until the 1962 amendment.

Measured by the standard employed by the Federal Drug Administration prior to the effective date of the 1962 amendment, the Court finds that the plaintiff's bioflavonoids were "safe," as that word was then understood.

All of the expert witnesses, including those called by the Government, were of the opinion that the plaintiff's bioflavonoids were innocuous when taken by anyone in any condition.

All agreed they were non-toxic and harmless per se in that a normal individual given such a product would not develop an adverse reaction, and were safe for use under the conditions prescribed, recommended or suggested in the labeling—that is, abnormal capillary permeability and fragility—The plaintiff's experts went further—They said the plaintiff's bioflavonoids were not only safe but were quite effective, when used as recommended, in certain types of capillary bleeding.

The Government's experts contend that the safety of a drug can only be determined by its efficacy—a "safe drug" becomes "unsafe" when used in place of the proper drug—the harm comes from the failure to use the best known drug for the treatment of the ailment complained of. This may or may not be so under the 1962 amendment—the Court does not determine that question here.

This decision is limited solely to the determination of whether

[1] 21 U.S.C. § 321(u).

the plaintiff's drugs are entitled to the exemption set forth in § 107(c)(4) of the Act.

The Clerk will send a copy of this order and memorandum opinion to all counsel of record.

(S) OREN R. LEWIS,
United States District Judge.

April 1, 1971

In the United States Court of Appeals for the Fourth Circuit

No. 71-1596

USV PHARMACEUTICAL CORPORATION, *Appellee,*

v.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION, WELFARE, AND HERBERT L. LEY, JR., COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, *Appellants.*

Appeal from the United States District Court for the Eastern District of Virginia, at Alexandria. Oren R. Lewis, District Judge.

(Argued December 8, 1971. Decided May 24, 1972.)

Before WINTER, RUSSELL and FIELD, Circuit Judges

Howard S. Epstein, Attorney, Department of Justice, (Richard W. McLaren, Assistant Attorney General, Bruce B. Wilson, C. Coleman Bird, and Cheryl S. Karner, Attorneys, Department of Justice, and Peter Barton Hutt, Assistant General Counsel, Joanne S. Sisk, Richard S. Silverman, Attorneys, Food, Drugs, and Environmental Health Division, Department of Health, Education, and Welfare, on brief) for Appellants, and Joel Hoffman (Robert L. Wald, Selma M. Levine, and Wald, Harkrader, Nicholson and Ross on brief) for Appellee.

RUSSELL, Circuit Judge:

Unlike the drug manufacturers in *Bentex*,[1] this plaintiff markets a line of citrus bioflavonoid drugs,[2] of which all but

[1] *Bentex Pharmaceuticals, Inc.* v. *Richardson*, No. 71-1243 (4th Cir., appeal docketed March 11, 1971).

[2] "Bioflavonoid" is defined in Dorland's Illustrated Medical Dictionary, 2d Edition, as follows: "a generic term for a group of compounds which are

two were covered by NDAs issued at various times in 1955 and 1956. Like the plaintiffs in *Bentex*, however, it seeks by an action for declaratory judgment to secure the benefit of the exemption available under the "grandfather clause" [3] from the enlarged definition of a "new drug" included in the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act of 1938. The defendants, who are the Secretary of Health, Education and Welfare (hereinafter referred to as HEW) and the Commissioner of the Food and Drug Administration (hereafter referred to as Commissioner), urge that jurisdiction should be refused on two grounds: 1. Primary jurisdiction lies with HEW; and 2. Failure to exhaust administrative remedies. They, also, attack the right of the plaintiff to claim the exemption. The District Court sustained jurisdiction and, largely on the basis of a Stipulation of Facts, upheld plaintiff's right to the statutory exemption both for its NDA'd and its non-NDA'd drugs. We reverse.

The threshold question raised by the defendants and overruled by the District Court may be quickly disposed of. Under similar circumstances in *Bentex*, we sustained the right of the District Court to entertain an action for declaratory judgment. We reach the same result here. Since we dismiss the claim of the plaintiff for exemption on behalf of its drugs on substantive grounds, it is unnecessary to consider the additional objection that plaintiff has failed to exhaust administrative remedies.

The substantive issue posed by this action is the right of the plaintiff to the exemption provided by Section 107(c)(4) from the revised definition of "new drug" incorporated in the 1962 Amendments. In resolving that issue, we must differentiate, even as the "grandfather clause" itself does, between the plaintiff's drugs, which were covered by an "effective NDA",[4] and those, which were marketed without an NDA. The Act makes a distinction in "grandfather" rights between a drug marketed under an NDA[5] and one marketed without an NDA. In the case

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widely distributed in plants and animals and which are concerned with maintenance of a normal state of the walls of small blood vessels." Stipulation of Facts, #4.

[3] Section 107(c)(4), Pub. L. 87-781 (1962), 21 U.S.C., 1972 Supplement, pp. 191-2.

[4] "Effective", as used in this phrase, means simply approved. Hagan. *Grandfather Protection Under the Drug Amendments of 1962*, 19 Food Drug Cosm., L. J., 119, p. 121.

[5] This is the term used to describe an approved preclearance application under Section 355.

of a drug covered by a previously approved NDA, the 1962 Amendments required the Secretary to withdraw the approved NDAs if after notice and opportunity of hearing, the applicant failed to file substantial evidence [6] that the drug previously approved is both safe and effective.[7] For such drugs, however, a grace period or temporary "grandfather right" was granted. Under it, the manufacturer was given two years within which to develop his showing of effectiveness and, during this period, the Secretary was prohibited from withdrawing or suspending the previously granted NDA.[8] On the other hand, a non-NDA'd drug which met the criteria stated in Section 107(c)(4) was exempted permanently from the amended definition of "new drug" made by the 1962 Amendments and was thereby relieved of securing an approved NDA as a condition for marketing clearance. The statutory criteria for this permanent "grandfather" exemption are stated as "any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined in Section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under Section 505 of that Act".

It is the contention of the plaintiff that all its drugs in question, both those previously NDA'd and those not, are protected by the permanent "grandfather clause" (i.e., Section 107(c)(4)). Because the statute seemingly makes a distinction between the two, it is proper to consider separately the two groups of drugs: i.e., those having NDAs and those without NDAs.

Taking up first plaintiff's NDA'd drugs: There is no dispute that such drugs met criteria (A) and (B), as set forth in the "grandfather clause", but the defendants seriously dispute the claim that they meet condition (C). Facially at least, this contention of the defendants seems unanswerable. These drugs are "covered by an effective application" or NDA, and are thus specifically barred by condition (C) from qualifying for exemption from the application of the effectiveness Amendments of 1962. The District Court found, however, that before "the day immediately preceding the enactment date", which was October 9, 1962, the previously granted NDAs had been effectively and practically withdrawn and that accordingly the drugs were not covered by an effective NDA on the crucial date of Octo-

[6] "Substantial evidence" is defined in the Act (21 U.S.C. 355(d)).
[7] Section 355(e), 21 U.S.C.
[8] Section 107(c)(3)(B), 21 U.S.C., note foll. Section 321.

ber 9, 1962. The error in this reasoning, however, is that it assumes that a manufacturer may effect a withdrawal of an effective NDA, either by a formal notice or by discontinuing compliance with the reporting requirements for NDA'd drugs. While an applicant may, during the pendency of his application, withdraw his application, he has no such right after approval of the application by the Secretary. At that point only the Secretary can withdraw the approval. As one commentator has accurately summed up, "It is true that a manufacturer may withdraw a pending NDA. Sec. 21 C.F.R. sec. 130.8 (1971). However, no provision in the law permits a manufacturer to withdraw an effective NDA; only FDA can do so through Section 505(e) procedure".[9] Prior to October 9, 1962, there was in this case no proceeding by FDA under Section 505(e) with reference to plaintiff's NDA'd drugs and there was accordingly no valid withdrawal of the plaintiff's effective NDAs, on or before the enactment date of the 1962 Amendments.

The plaintiff, though, presses another theory upon the basis of which it claims the previously issued NDAs are to be regarded as ineffective on October 9, 1962. Thus it argues that its pre-1962 NDA'd drugs became generally recognized as safe on or before October 9, 1962. So much the defendants seem to concede in the Stipulation of Facts submitted to the District Court. From this fact, it reasons that its NDA drugs ceased to be "new drugs" as defined in the Act, on or before October 9, 1962, and, ergo, its previously issued NDAs were no longer needed or "effective" on the critical date of October 9.[10] The difficulty with this argument, plausible though it may be, is that it would make surplusage of requirement (C) in the exemption statute. Thus, if a drug met the test set up in (B), that is, was generally recognized as safe on October 9, 1962, it would not be necessary, under the plaintiff's argument, to consider whether (C) was applicable or not. Such a construction of the exemption statute, under which a clearly stated condition to its application is to be treated as a nullity, offends the well-settled rule of statutory construction that all parts of a statute are to be given effect if at all possible.[11] It is manifestly

[9] Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185 at p. 198, n. 77 (1971).

[10] See Barth, *Following the NAS-NRC Effectiveness Review, What?*, 22 Business Lawyer, 1185, 1187 (1967).

[11] *Jarecki* v. *G. D. Searle & Co.* (1961) 367 U.S. 303, 307; *Ginsberg & Sons* v. *Popkin* (1932) 285 U.S. 204, 208.

possible to give effect to the conditions enunciated in both (B) and (C). There are many drugs that satisfy both conditions, that is, are generally recognized as safe and effective and are being marketed without an approved NDA. There is nothing inconsistent in the two requirements. Moreover, condition (C) represented a limitation on the right to an exemption that the Congress clearly and unmistakably intended to apply. The Congress never intended that a drug being marketed under an approved NDA might qualify under the "grandfather clause." This is plain from the comment in the Conference Committee Report that the exemption was to apply "to existing labeling claims of drugs *that have never previously been subject to the new-drug procedure*". (Italics added.) H.R. Rep. 2526, 87th Cong., 2d Sess., p. 23. Moreover, the argument of the plaintiff would run counter to the principle that statutory exemptions, particularly as applied to statutes concerned with public health and safety, are to be strictly and narrowly construed.[12]

The plaintiff has, however, two drugs,[13] involved in this proceeding, which were generally recognized as safe and were[14] marketed as "old drugs" without an approved NDA on October 9, 1962. These drugs, as we earlier indicated, present separate problems from those drugs for which there are approved NDAs. They fall into the category of what are generally described in the trade as "me-too" drugs.[15] Such a drug, if generally regarded as safe on October 9, 1962, meets literally the criteria for exemption stated in the "grandfather clause". To sustain the exemption, however, creates an inequitable result, provided the pioneer drug was NDA'd. In that event, the pioneer drug would be subject to withdrawal of marketing privilege absent substantial evidence of effectiveness, whereas its copy would enjoy immunity from any such requirement under Section 107(c)(4). Most commentators, while admitting the incongruity of this result, justify it as one compelled by the literal

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[12] *United States* v. *Allan Drug Corporation* (10th Cir. 1966) 357 F. 2d 718, 718, cert. denied 385 U.S. 899.

[13] Duo-C.V.P. with Vitamin K Capsules and Bivam.

[14] Stipulation of Facts, Number 17.

[15] A "me-too" drug is generally defined as "one which is equivalent to another, pioneer drug, which preceded it on the market." Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 198, n. 78. (1971).

language of the statute.[16] Their reasoning is similar to that of the Court in *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 542, where speaking to a somewhat illogical provision in this same Act, Judge Friendly said: "A sufficient answer is the simple if not altogether satisfying one that Congress said so" [17] The FDA itself has recognized the vexing problem presented by the "me-too" drug and has sought to resolve it by a change in its position on the scope and application of an NDA.

It is the contention of the FDA that an approved NDA covers not merely the marketing of the parent but also its "me-too" offsprings and for that reason the "me-too" drugs have been permitted to be marketed without an NDA. Accordingly, under this theory, the withdrawal of the approved NDA of the pioneer operates as a withdrawal of marketing rights for the "me-too", unless the latter, either individually or in conjunction with its pioneer, provides substantial evidence of effectiveness. This view has, however, been severely criticized and with considerable reason. It is, as one critic has observed, "at variance with the uniform position it (FDA) has taken over the years with regard to the nature of NDAs." This position, which is termed the "personal approach" holds that "Section 505 applies to drugs as individual articles, not as collective groups, and that each manufacturer of a new drug must file his own NDA." This critic concludes with the observation that it is "an unjustifiable exercise in semantics to say that a drug legally marketed without an NDA was 'covered' by the NDA of another manufacturer's drug." [18]

That the policy of FDA has heretofore been contrary to the position now taken by it is further illustrated by the circum-

[16] See, Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 203 (1971):

> Surely, me-too drugs never processed through the new procedures satisfy all the requirements of section 107(c)(4).

To the same effect is Hagan, *Grandfather Protection Under the Drug Amendments of 1962*, 19 Food Drug Cosm. L.J., 119, at pp. 125–6. D'Andrade, *The Effect of NAS-NRC Review on Me-Too and Post-'62 Drugs*, 25 Food, Drug. Cosm. L.J., 330, 334 (1970).

[17] This, of course, is not the only inequity in the Amendments. There are other inequities, as FDA freely conceded at a House Hearing before a Subcommittee of the Commission on Government Operations on Drug Efficacy, Part 2, 91st Cong., 1st Sess. (1969), pp. 384–5.

[18] Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 203, n. 111 (1971).

stances under which at least one of the "me-toos" of the plaintiff began marketing. Prior to marketing Bivam, one of its "me-toos" similar in formula to other drugs previously NDA'd by it, the plaintiff inquired of FDA whether it was an "old drug" entitled to be marketed without an NDA. FDA, after reviewing its composition and labeling, advised the plaintiff it was a product "generally regarded as safe" (and thus an "old drug") and could be marketed without an NDA. There was no suggestion by the plaintiff that it sought to market this drug under any previous NDA granted one of its products nor did the FDA base its advice on that basis. Both the plaintiff and FDA assumed at that time that a "me-too" drug, which had become generally recognized as safe, was entitled to be marketed without an NDA; in short, that the qualification for marketing a "me-too" drug was general recognition of safety and not the NDA of its pioneer.

It would seem that the consistent construction of the Act by the FDA for thirty years [19] and a construction which accords with the literal language of the Act itself may only be changed by Congress itself.[20] In fact, the General Counsel of FDA, in testimony before a House Subcommittee Hearing on Drug Efficacy, Part 2 (91st Cong., 1st Sess., 1969) p. 375, expressed the wish that Congress would "pass" a clarifying amendment on this issue, conceding that the position of his agency was in considerable doubt.

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[19] See, Hagan, *supra*, at p. 125:

> Furthermore, the concept that new drug clearance by one manufacturer affects the rights of subsequent manufacturers is inconsistent with the established doctrine that new drug clearance is *personal* to the applicant, and does not embrace the drug *per se*.

[20] Cf., comment in Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal 185, at pp. 206–7 (1971):

> Ultimately the issue of the status of me-too drugs will have to be squarely faced, and the FDA interpretation of section 107(c)(4), holding that they follow the pioneer's fate, should be repudiated by the courts. In that event the agency will undoubtedly ask Congress for new legislation to remedy the situation. In view of the obvious inequities in the present situation, this would seem to be the most desirable solution.

But even if it be assumed that "me-too" drugs are generally entitled to Section 107(c)(4) protection, provided they were generally recognized as safe on October 9, 1962, that does not resolve the right of the plaintiff's "me-toos" to exemption. As has been pointed out, the reasoning on which "me-toos" are regarded as not covered by the NDAs granted the manufacturers of their pioneers is that an NDA is regarded as "personal" to the manufacturer submitting the application and to the drug covered. But in this case, the "me-toos" are similar in formula and labeling to other drugs for which the plaintiff itself applied and obtained NDAs. It is true that, in the case of one drug at least, to which reference has already been made, plaintiff's "me-toos" were regarded as exempt, not because plaintiff had an approved NDA for a similar drug, but because FDA was of the opinion that it met the requirements for classification as an old drug. Nonetheless, it is the "personal" character of the NDA that has been deemed as the basis on which it is contended that the "me-toos" are not covered by the NDA granted another manufacturer, albeit the drugs involved may be similar. That reasoning manifestly cannot sustain a right of exemption in favor of plaintiff's "me-toos". The plaintiff's NDAs, being "personal" to it, would cover all its products similar in formula, including those specifically described in its applications and all others like in formula. The similarity in formula, between plaintiff's NDA'd drugs and its "me-toos" is stipulated. Under those circumstances, both the NDA'd and the "me-too" drugs will be treated alike and neither can qualify for exemption under the terms of Section 107(c)(4). It is recognized that this conclusion places the plaintiff in a less favorable position than that occupied by others who may have copied its product prior to October 9, 1962. That inequity is, however, inherent in the law and may only be redressed by Congress, not by the Courts under the guise of construction.

Reversed, with directions to enter judgment for the defendants.

REVERSED.

495-151—78——31

[*Filed May 24, 1972*]

JUDGMENT

IN THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 71-1596

USV PHARMACEUTICAL CORPORATION, APPELLEE,

v.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, AND HERBERT L. LEY, JR., COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, APPELLANTS.

Appeal from the United States District Court for the Eastern District of Virginia

This cause came on to be heard on the record from the United States District Court for the Eastern District of Virginia, and was argued by counsel.

On CONSIDERATION WHEREOF, It is now here ordered and adjudged by this Court that the judgment of the said District Court appealed from, in this case, be, and the same is hereby, reversed.

SAMUEL W. PHILLIPS, *Clerk.*

In the Supreme Court of the United States

No. 72-666

USV PHARMACEUTICAL CORPORATION, PETITIONER,

v.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE, ET AL.

ORDER ALLOWING CERTIORARI. Filed January 8, 1973.

The petition herein for a writ of certiorari to the United States Court of Appeals for the Fourth Circuit is granted. The case is consolidated with Nos. 72-394, 72-414, 72-528 and 72-555, and a total of three hours is allotted for oral argument.

Relevant Statutes and Regulations

The Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040, as amended by the Harris-Kefauver Act, 76 Stat. 780, 21 U.S.C. 301 *et seq.*:

Sec. 201 [321]. For the purposes of this Act—

* * * * *

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

* * * * *

Sec. 301 [331]. The following acts and the causing thereof are hereby prohibited:

(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.

* * * * *

(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 404 or 505.

* * * * *

Sec. 302 [332]. (a) The district courts of the United States and the United States courts of the Territories shall have juris-

Note—References in brackets [ ] are to title 21 U.S. Code.

diction, for cause shown, and subject to the provisions of section 381 (relating to notice to opposite party) of Title 28, to restrain violations of section 301 of this title, except paragraphs (h), (i), and (j) of said section.

* * * * *

SEC. 303 [333]. (a) Any person who violates a provision of section 301 shall be imprisoned for not more than one year or fined not more than $1,000, or both.

* * * * *

SEC. 304 [334]. (a) (1) Any article of food, drug, device, or cosmetic that is adulterated or misbranded when introduced into or while in interstate commerce or while held for sale (whether or not the first sale) after shipment in interstate commerce, or which may not, under the provisions of section 404 or 505, be introduced into interstate commerce, shall be liable to be proceeded against while in interstate commerce, or at any time thereafter, on libel of information and condemned in any district court of the United States or United States court of a Territory within the jurisdiction of which the article is found: *Provided, however,* That no libel for condemnation shall be instituted under this Act, for any alleged misbranding if there is pending in any court a libel for condemnation proceeding under this Act based upon the same alleged misbranding, and not more than one such proceeding shall be instituted if no such proceeding is so pending, except that such limitations shall not apply (A) when such misbranding has been the basis of a prior judgment in favor of the United States, in a criminal, injunction, or libel for condemnation proceeding under this Act, or (B) when the Secretary has probable cause to believe from facts found, without hearing, by him or any officer or employee of the Department that the misbranded article is dangerous to health, or that the labeling of the misbranded article is fraudulent, or would be in a material respect misleading to the injury or damage of the purchaser or consumer. In any case where the number of libel for condemnation proceedings is limited as above provided the proceeding pending or instituted shall, on application on the claimant, seasonably made, be removed for trial to any district agreed upon by stipulation between the parties, or, in case of failure to so stipulate within a reasonable time, the claimant may apply to the court of the district in which the seizure has been made, and such court (after giving

the United States attorney for such district reasonable notice and opportunity to be heard) shall by order, unless good cause to the contrary is shown, specify a district of reasonable proximity to the claimant's principal place of business to which the case shall be removed for trial.

(2) The following shall be liable to be proceeded against at any time on libel of information and condemned in any district court of the United States or United States court of a Territory within the jurisdiction of which they are found: (A) Any drug that is a counterfeit drug, (B) Any container of a counterfeit drug, and (C) Any punch, die, plate, stone, labeling, container, or other thing used or designed for use in making a counterfeit drug or drugs.

* * * * *

SEC. 505 [355]. (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by

written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness

of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is presented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact: *Provided,* That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j), or the applicant has refused to permit access

to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

* * * * *

(h) An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for

leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

* * * * *

SECTION 107 (C) OF PUBLIC LAW 87–781, 76 STAT. 788–789, NOTE FOLLOWING 21 U.S.C. 321 (1970 ED.):

SEC. 107(c)(1) As used in this subsection, the term "enactment date" means the date of enactment of this Act; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.

(2) An application filed pursuant to section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date by virtue of paragraph (2) of this subsection—

(A) the amendments made by this Act to section 201(p), and to subsections (b) and (d) of section 505, of the basic Act insofar as such amendments relate to the effectiveness of drugs shall not, so long as approval of such

application is not withdrawn or suspended pursuant to section 505(e) of that Act, apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application, but shall apply to any changed use, or conditions of use, prescribed, recommended, or suggested in its labeling, including such conditions of use as are the subject of an amendment or supplement to such application pending on, or filed after, the enactment date; and

(B) clause (3) of the first sentence of section 505(e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application (except with respect to such use, or conditions of use, as are the subject of an amendment or supplement to such approved application, which amendment or supplement has been approved after the enactment date under section 505 of the basic Act as amended by this Act) until whichever of the following first occurs: (i) the expiration of the two-year period beginning with the enactment date; (ii) the effective date of an order under section 505(e) of the basic Act, other than clause (3) of the first sentence of such section 505(e), withdrawing or suspending the approval of such application.

(4) In the case of any drug which, on the first day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, 52 STAT. 1040, PRIOR TO THE HARRIS-KEFAUVER AMENDMENT OF 1962 (21 U.S.C. 301 ET SEQ. (1958 ED.)):

SEC. 201[321]. For the purposes of this chapter—

* * * * *

(p) The term "new drug" means—

(1) Any drug the composition of which is such that such

drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this chapter it was subject to former sections 1–5 and 7–15 of this title, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug the composition of which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

* * * * *

SEC. 505 [355]. (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an application filed pursuant to subsection (b) of this section is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) An application provided for in subsection (b) of this section shall become effective on the sixtieth day after the filing thereof unless prior to such day the Secretary by notice to the applicant in writing postpones the effective date of the application to such time (not more than one hundred and eighty days after the filing thereof) as the Secretary deems necessary to enable him to study and investigate the application.

(d) If the Secretary finds, after due notice to the applicant and giving him an opportunity for a hearing, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; or (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions, he shall, prior to the effective date of the application, issue an order refusing to permit the application to become effective.

(e) The effectiveness of an application with respect to any drug shall, after due notice and opportunity for hearing to the applicant, by order of the Secretary be suspended if the Secretary finds (1) that clinical experience, tests by new methods, or tests by methods not deemed reasonably applicable when such application became effective show that such drug is unsafe for use under the conditions of use upon the basis of which the application became effective, or (2) that the application contains any untrue statement of a material fact. The order shall state the findings upon which it is based.

* * * * *

THE ADMINISTRATIVE PROCEDURE ACT, 80 STAT. 381 (5 U.S.C. 551 *ET SEQ.*)

§ 554. Adjudications.

(a) This section applies, according to the provisions thereof, in every case of adjudication required by statute to be determined on the record after opportunity for an agency hearing, except to the extent that there is involved—

(1) a matter subject to a subsequent trial of the law and the facts de novo in a court;

(2) the selection or tenure of an employee, except a hearing examiner appointed under section 3105 of this title;

(3) proceedings in which decisions rest solely on inspections, tests, or elections;

(4) the conduct of military or foreign affairs functions;

(5) cases in which an agency is acting as an agent for a court; or

(6) the certification of worker representatives.

(b) Persons entitled to notice of an agency hearing shall be timely informed of—

(1) the time, place, and nature of the hearings.

(2) the legal authority and jurisdiction under which the hearing is to be held; and

(3) the matters of fact and law asserted.

When private persons are the moving parties, other parties to the proceeding shall give prompt notice of issues controverted in fact or law; and in other instances agencies may by rule require responsive pleading. In fixing the time and place for hearings, due regard shall be had for the convenience and necessity of the parties or their representatives.

(c) The agency shall give all interested parties opportunity for—

(1) the submission and consideration of facts, arguments, offers of settlement, or proposals of adjustment when time, the nature of the proceeding, and the public interest permit; and

(2) to the extent that the parties are unable so to determine a controversy by consent, hearing and decision on notice and in accordance with sections 556 and 557 of this title.

(d) The employee who presides at the reception of evidence pursuant to section 556 of this title shall make the recommended decision or initial decision required by section 557 of this title, unless he becomes unavailable to the agency. Except to the extent required for the disposition of ex parte matters as authorized by law, such an employee may not—

(1) consult a person or party on a fact in issue, unless on notice and opportunity for all parties to participate; or

(2) be responsible to or subject to the supervision or direction of an employee or agent engaged in the perform-

ance of investigative or prosecuting functions for an agency.

An employee or agent engaged in the performance of investigative or prosecuting functions for an agency in a case may not, in that or a factually related case, participate or advise in the decision, recommended decision, or agency review pursuant to section 557 of this title, except as witness or counsel in public proceedings. This subsection does not apply—

(A) in determining applications for initial licenses;

(B) to proceedings involving the validity or application of rates, facilities, or practices of public utilities or carriers; or

(C) to the agency or a member or members of the body comprising the agency.

(e) The agency, with like effect as in the case of other orders, and in its sound discretion, may issue a declaratory order to terminate a controversy or remove uncertainty.

§ 702. Right of review.

A person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action within the meaning of a relevant statute, is entitled to judicial review thereof.

§ 703. Form and venue of proceeding.

The form of proceeding for judicial review is the special statutory review proceeding relevant to the subject matter in a court specified by statute or, in the absence or inadequacy thereof, any applicable form of legal action, including actions for declaratory judgments or writs of prohibitory or mandatory injunction or habeas corpus, in a court of competent jurisdiction. Except to the extent that prior, adequate, and exclusive opportunity for judicial review is provided by law, agency action is subject to judicial review in civil or criminal proceedings for judicial enforcement.

§ 704. Actions reviewable.

Agency action made reviewable by statute and final agency action for which there is no other adequate remedy in a court are subject to judicial review. A preliminary, procedural, or intermediate agency action or ruling not directly reviewable is subject to review on the review of the final agency action. Except as otherwise expressly required by statute, agency action otherwise final is final for the purposes of this section whether

or not there has been presented or determined an application for a declaratory order, for any form of reconsiderations, or, unless the agency otherwise requires by rule and provides that the action meanwhile is inoperative, for an appeal to superior agency authority.

21 C.F.R. 130.12(a)(5) as amended, 35 F.R. 7251, May 8, 1970, provides:

(a) If the Commissioner determines upon the basis of the application, or upon the basis of other information before him with respect to the new drug, that * * *

(5)(i) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(ii) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is "substantial evidence" to support the claims of effectiveness for "new drugs" and antibiotic drugs.

(*a*) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:

(1) A clear statement of the objectives of the study.

(2) A method of selection of the subjects that—

(*i*) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of suscepti-

bility and exposure to the condition against which prophylaxis is desired.

(*ii*) Assigns the subjects to test groups in such a way as to minimize bias.

(*iii*) Assures comparability in test and control groups of pertinent variables, such as age, sex, severity, or duration of disease, and use of drugs other than the test drug.

(3) Explains the methods of observation and recording of results, including the variables measured, quantitation, assesament of any subjective response, and steps taken to minimize bias on the part of the subject and observer.

(4) Provides a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. Level and methods of "blinding," if used, are to be documented. Generally, four types of comparison are recognized:

(*i*) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients.

(*ii*) Placebo control: Comparison of the results of use of the new drug entity with an inactive preparation designed to resemble the test drug as far as possible.

(*iii*) Active treatment control: An effective regimen of therapy may be used for comparison, e.g., where the condition treated is such that no treatment or administration of a placebo would be contrary to the interest of the patient.

(*iv*) Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in

certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen (therapeutic, diagnostic, prophylactic) the effectiveness of which is established.

(5) A summary of the methods of analysis, and and evaluation of data derived from the study, including any appropriate statistical methods.

Provided, however, That any of the above criteria may be waived in whole or in part, either prior to the investigation or in the evaluation of a completed study, by the Director of the Bureau of Drugs with respect to a specific clinical investigation; a petition for such a waiver may be filed by any person who would be adversely affected by the application of the criteria to a particular clinical investigation; the petition should show that some or all of the criteria are not reasonably applicable to the investigation and that alternative procedures can be, or have been, followed, the results of which will or have yielded data that can and should be accepted as substantial evidence of the drug's effectiveness. A petition for a waiver shall set forth clearly and concisely the specific provision or provisions in the criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been, employed, what results have been obtained, and the basis on which it can be, or has been, concluded that the clinical investigation will or has yielded substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(*b*) For such an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(*c*) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the

approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

(6) Based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; the Commissioner shall within 180 days after the filing of the application inform the applicant in writing of his intention to issue a notice of hearing on a proposal to refuse to approve the application.

(b) Unless by the 30th day following the date of issuance of the letter informing the applicant of the intention to issue a notice of hearing, the applicant.

(1) Withdraws the application; or

(2) Waives the opportunity for a hearing; or

(3) Agrees with the Commissioner on an additional period to precede issuance of such notice of hearing,

the Commissioner shall expeditiously notify the applicant of an opportunity for a hearing on the question of whether such application is approvable as provided in § 130.14.

21 C.F.R. 130.14, as amended, 35 F.R. 7252, May 8, 1970, provides:

(a) The notice to the applicant of opportunity for a hearing on a proposal by the Commissioner to refuse to approve an application or to withdraw the approval of an application will specify the grounds upon which he proposes to issue an order. On request of the applicant, the Commissioner will explain the reasons for his action. The notice of hearing will be published in the Federal Register and will specify that the applicant has 30 days after issuance of the notice within which he is required to file a written appearance electing whether:

(1) To avail himself of the opportunity for a hear-

ing at the place specified in the notice of hearing; or

(2) Not to avail himself of the opportunity for a hearing.

(b) If the applicant elects to avail himself of the opportunity for a hearing, he is required to file a written appearance requesting the hearing within 30 days after the publication of the notice and giving the reason why the application should not be refused or should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition to the notice of opportunity for a hearing. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data. If a hearing is requested and is justified by the applicant's response to the notice of hearing, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence, not more than 90 days after the expiration of such 30 days unless the hearing examiner and the applicant otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval.

(c) The hearing will be open to the public: *Provided, however,* That if the Commissioner finds that portions of the application which serve as a basis for the hearing contain information concerning a method or process which as a trade secret is entitled to protection, the part of the hearing that involves such portions will not be public unless the respondent so specifies in his appearance.

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In the Supreme Court of the United States

OCTOBER TERM, 1972

No.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, PETITIONERS

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

The Solicitor General, on behalf of the Secretary of Health, Education, and Welfare and the Commissioner of Food and Drugs, petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Fourth Circuit in this case.

OPINIONS BELOW

The opinion of the court of appeals (App. A, *infra*, pp. 1a–11a) is not yet officially reported. The order of the Commissioner of Food and Drugs was published in the Federal Register on June 18, 1971 (36 Fed. Reg. 11763) (App. C, *infra*, pp. 14a–22a).

JURISDICTION

The judgment of the court of appeals was entered on May 24, 1972 (App. B, *infra*, pp. 12a–13a). Mr. Justice Rehnquist extended the time within which to file a petition for certiorari to September 7, 1972. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1) and 21 U.S.C. 355(h).

QUESTIONS PRESENTED

Whether the Commissioner of Food and Drugs may, in implementing the drug effectiveness requirements of the 1962 amendments to the Food, Drug, and Cosmetic Act of 1938, withdraw approval for the marketing of a drug for lack of proof of effectiveness without a hearing, if the manufacturer has failed to comply with the Commissioner's regulations requiring that a request for hearing must be supported by the kind of "substantial evidence" of effectiveness required by the statute.

STATUTORY PROVISIONS AND REGULATIONS INVOLVED

Section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) provides in pertinent part:

> The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds * * * (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug

> will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof * * *.

Section 505(d) (21 U.S.C. 355(d)) provides in pertinent part:

> * * * As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof.

Pertinent provisions of the regulations of the Commissioner of Food and Drugs, 21 C.F.R. 130.12(a)(5) and 130.14, as amended, 35 Fed. Reg. 7251, 7252, are set forth in Appendix D, *infra*, pp. 23a–28a.

STATEMENT

1. *Background.* This case arises out of efforts by the United States Food and Drug Administration (FDA) to insure that all drugs available to the public are effective for their intended uses. Prior to 1962, the Federal Food, Drug, and Cosmetic Act of 1938, 52 Stat. 1052, required only that the sponsor of a new drug provide evidence that the product was safe for its intended uses in order to obtain FDA approval for

marketing. This was one of the major deficiencies in the Act which Congress sought to remedy in the Harris-Kefauver Drug Amendments of 1962, 76 Stat. 781. Section 201(p) of the Act was amended to define a "new drug" as one not generally recognized by qualified experts as safe *and effective* for its intended uses (21 U.S.C. 321(p)(1)). Under Section 505(e) (21 U.S.C. 355(e)), the agency was given authority to withdraw approval of new drug applications (NDAs) previously granted if the NDA holder cannot provide "substantial evidence" of the drug's effectiveness. "Substantial evidence" is defined in the statute to mean "adequate and well controlled investigations, including clinical investigations" by scientific experts, on the basis of which effectiveness could be determined (Section 505(d)). Transitional provisions in the 1962 amendments provided that holders of previously approved NDAs would not be required to produce proof of effectiveness for two years (P.L. 81-781, Section 107(c)(3)(B), 76 Stat. 788-789). This "grace period" was intended to permit drug manufacturers to undertake necessary clinical investigations to develop evidence of effectiveness, which they had not previously been required to have.[1]

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[1] The amendments also afforded an exemption from the effectiveness requirement for drugs which were commercially marketed on the enactment date, which were not covered by an effective NDA, and which were not "new drugs" as defined by the Act prior to amendment. P.L. 87-781, Section 107(c)(4), 76 Stat. 789. Respondent's claim to an exemption under this "grandfather clause" was rejected below by both the Commissioner (App. C, *infra*, p. 17a) and the court of appeals (App. A, *infra*, p. 6a).

To assist FDA in the enormous task of reviewing efficacy claims for all drugs approved between 1938 and 1962, the Commissioner of Food and Drugs, in 1966, contracted with the National Academy of Sciences-National Research Council (NAS–NRC) to establish expert panels to review such drugs on the basis of information submitted by the drug manufacturers. All NDA holders whose approval had been obtained on the basis of safety only were directed to submit to NAS–NRC "the best data available" to support claims made for their drugs. 31 Fed. Reg. 13014. When NAS–NRC completes its evaluation of a drug, it submits a report and recommendation to the Commissioner. On the basis of such reports and any other information indicating a lack of substantial evidence of effectiveness, the Commissioner can initiate procedures under Section 505(e) leading to possible withdrawal of approval. Between October 1967 and April 1969, 2,824 reports were submitted, covering approximately 3,700 drugs manufactured by 237 companies.[2]

It soon became apparent to FDA that it could not effectively deal with the large volume of drugs for which no substantial evidence of effectiveness was available if it proceeded under then-effective regulations, which afforded a full administrative hearing prior to withdrawal to any manufacturer making a timely request for one. Accordingly, on September 19, 1969, FDA published regulations defining the scientific content of studies which would constitute substan-

[2] National Academy of Sciences, Drug Efficacy Study, Final Report to the Commissioner of Food and Drugs, p. 5.

tial evidence within the meaning of Section 505(d), and limiting the right to a hearing to those applicants whose requests were supported by such evidence (34 Fed. Reg. 14596). On the same day, these new regulations were applied to a final order withdrawing approval of certain combination antibiotic drug products. The withdrawal order was affirmed on appeal, *Upjohn Co.* v. *Finch,* 422 F. 2d 944 (C.A. 6), but the agency was enjoined in another proceeding from further action under the regulations, because they had been published without affording interested parties an opportunity for comment. *Pharmaceutical Mfrs. Assn* v. *Finch,* 307 F. Supp. 858 (D. Del.). On May 8, 1970, after consideration of industry comments, the regulations were republished in amended form (35 Fed. Reg. 7250). These regulations (21 C.F.R. 130.12 (a)(5) and 130.14) were thereafter upheld as consistent with the statute and the requirements of due process. *Pharmaceutical Mfrs. Assn* v. *Richardson,* 318 F. Supp. 301 (D. Del.).[3]

2. *Proceedings Below.* In 1953, the Food and Drug Administration approved an NDA filed by Hynson, Westcott and Dunning, Inc., for a prescription drug,

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[3] Prior to the decision below in the instant case, actions taken by the Commissioner under the regulations governing summary withdrawal procedures and under parallel regulations for decertification of antibiotic drugs had been uniformly upheld in the courts of appeals. See *Ciba-Geigy Corp.* v. *Richardson,* 446 F. 2d 466 (C.A. 2); *Pfizer, Inc.* v. *Richardson,* 434 F. 2d 536 (C.A. 2); *Upjohn* v. *Finch, supra*; see also *American Cyanamid Co.* v. *Richardson,* 456 F. 2d 509 (C.A. 1) (opinion by Coffin, J., denying motion to stay order of withdrawal).

Lutrexin,[4] the active ingredient of which is lututrin, which is indicated for use in premature labor, threatened and habitual abortion, and dysmenorrhea. The agency advised the manufacturer that it doubted the drug's effectiveness for its intended uses (JA I, 1),[5] but, under the statute in effect at that time, it was obliged to approve the NDA based upon consideration of the drug's safety only.

Pursuant to the arrangement for review of effectiveness of drugs described above, an NAS–NRC panel evaluated Lutrexin for each of its recommended uses and reported to the Commissioner. Although the panel's stated conclusion was that the drug was "possibly effective," its comments made clear that it found a lack of adequate, controlled studies affording satisfactory evidence of the drug's effectiveness. It recommended that each claim be considered "inappropriate" or "unwarranted" unless documentation were provided (JA I, 7–8). On May 24, 1968, after review of these findings, the Commissioner published a notice inviting Hynson to submit additional evidence of the drug's claimed effectiveness (JA I, 11). On March 22, 1969, having considered additional material submitted but still finding no substantial evidence of effectiveness, the Commissioner published notice of his intention to withdraw approval of the drug and notice to

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[4] The administrative proceedings also involved a companion drug, Trexinest, the marketing of which has since been discontinued.

[5] "JA" refers to the two-volume Joint Appendix in the court of appeals.

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Hynson of its opportunity for a hearing prior to withdrawal (JA I, 13). At that time, the agency's rules still provided for a hearing upon timely request by any adversely affected party, and Hynson so requested (JA I, 16).

The hearing was never commenced, however. Instead, Hynson filed a complaint for declaratory and injunctive relief in the United States District Court for the District of Maryland, claiming to be exempt from the efficacy review provisions of the 1962 Drug Amendments (JA I, 17). On September 11, 1970, the district court dismissed that action, holding that the issues presented were within the primary jurisdiction of FDA and that Hynson had failed to exhaust its administrative remedies (JA I, 26). No appeal was taken from that judgment.

While the case was pending in the district court, FDA adopted its new regulations, discussed above, establishing standards for the submission of "substantial evidence" to furnish a basis for a hearing prior to withdrawal of approval. Parties subject to pending withdrawal proceedings were given additional time to supplement their original hearing requests to bring them into compliance with the new rules (JA I, 21). Hynson declined to amend its request, taking the position that its right to a hearing had already vested under the old rules applicable at the time of its original request (JA I, 23–24).

Following dismissal of its lawsuit, Hynson renewed its request for an administrative hearing (JA I, 27). Although continuing to claim an absolute right to a hearing under the old rules (JA I, 27–28), it also

listed what it contended was substantial evidence of Lutrexin's effectiveness (JA I, 30–35). This listing consisted primarily of material previously submitted to NAS–NRC or to FDA, supplemented by certain affidavits and reports of medical studies which had been submitted to the district court (JA I, 36–37).

On May 31, 1971, the Commissioner issued an order noticing withdrawal of new drug approval for Lutrexin, and, *inter alia,* denying Hynson's request for a hearing (App. C, *infra,* pp. 14a–22a). In denying a hearing, the Commissioner found that Hynson was obliged to comply with the currently applicable regulations (*id.* at 16a) and that it had failed to comply (*id.* at 17a). He pointed out that it had failed to identify what, if anything, in the mass of material submitted, it relied upon as "substantial evidence" of effectiveness. Most of that material had previously been considered by the NAS–NRC panel, and such studies as were included were unaccompanied by any of the documentation required by the new regulations to show that they were adequate and well-controlled. The Commissioner also dealt specifically with those published and unpublished studies cited by Hynson which had not previously been submitted to NAS–NRC or to the agency. He demonstrated how each showed deficiencies on its face that prevented it, under the rules, from being treated as an adequate and well-controlled study (*id.* at 17a–20a).

On appeal, the court of appeals set aside the withdrawal order. It found the "crucial" issue to be the statutory requirement of an opportunity for a hearing (App. A, *infra,* p. 6a). It purported not to question

the Commissioner's right to adopt regulations allowing denial of a hearing where no genuine and substantial issue of fact is presented, and it presumed, without explicitly deciding, that this case is governed by the rules in effect at the time of decision, not the time of Hynson's initial request for a hearing (*id.* at 7a). In holding that the test of whether a hearing must be held is "whether there is any 'genuine and substantial' evidence that supports the position of the applicant," the court apparently ascribed to the Commissioner an insistence that the evidence proffered actually prove effectiveness as a predicate to grant of a hearing (*id.* at 7a–8a). It pointed out that Congress adopted the test of "substantial" evidence as an intentionally milder test than "preponderant" or "conclusive" evidence (*id.* at 8a–9a).

The court held (*id.* at 9a):

> * * * the showing of the appellant was such that, under a reasonable construction of the Commissioner's own regulations, as well as under familiar principles of due process, and the requirements of the Administrative Procedure Act, it was entitled to an impartial hearing before its NDA was withdrawn. * * *

The court relied upon several factors: the "possibly effective" rating given the drug by the NAS–NRC panel; the absence of any record evidence of ineffectiveness; the studies and opinions of medical experts of impressive credentials; and the affidavit of a former FDA medical officer that in his opinion Hynson had submitted adequate and well-controlled clinical investigations (*id.* at 9a–10a). The Commissioner's

efforts to demonstrate that deficiencies in Hynson's evidence made it inadequate under the statutory requirement for "adequate and well-controlled" studies were held to be unavailing. Such questions, the court held, are to be resolved in an adversary hearing (*id.* at 11a).

REASONS FOR GRANTING THE WRIT

1. It was the plain purpose of Congress, in the 1962 amendments to the Federal Food, Drug, and Cosmetic Act of 1938, to afford assurance to the American consumer that all drugs available on the market are both safe and effective for their intended uses. The Senate Committee on the Judiciary was "of the opinion that with [the] changes [it proposed] the legislation will insure the reliability of drugs" (S. Rep. No. 1744, Part II, 87th Cong., 2d Sess., p. 1). To achieve this end, Congress deliberately placed a heavy and precisely defined burden upon the drug manufacturer to prove the effectiveness of a drug it seeks to market by requiring that claims of effectiveness for new drugs be supported by "substantial evidence" (Section 505 (e)). Only evidence of a particular kind was declared to be "substantial," *viz.*: "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved * * *" (Section 505(d)).

That the choice of this exacting standard was purposeful is apparent from a review of the legislative history. An impressive succession of scientific experts testified that the opinion evidence of physicians testi-

fying only from observation and personal experience is an inherently unreliable indicator of drug effectiveness. These witnesses persuaded Congress to insist upon adequate and well-controlled clinical investigations in support of claims of drug efficacy. This legislative history has been exhaustively considered by courts that have upheld the statutory standard and the Commissioner's interpretive rules thereunder. See *Upjohn Co.* v. *Finch*, *supra*, 422 F.2d at 950–954; *Pharmaceutical Mfrs. Assn* v. *Richardson*, *supra*, 318 F. Supp. at 306–309.

The Commissioner's congressionally assigned responsibility to remove ineffective drugs from the market presents an enormous task, involving evaluation of more than 4,000 drug products (and approximately 16,700 separate claimed uses for the products) that had been granted approved NDAs between 1938 and 1962. Evaluation of these products, with the assistance of NAS–NRC, has led to the initial conclusion that approximately 2,800 are effective for at least one claimed use, 200 are "probably effective," 600 are "possibly effective," and 550 are ineffective.[6] Drug products in any category other than "effective" are potentially subject to withdrawal of approval unless their effectiveness can be established in accordance with the statutory standard. FDA has thus been faced with the problem of dealing with 1,350 suspect drug products (not to mention the numerous other

[6] With respect to claims, FDA estimates that approximately 12,500 of the 16,700 claims made for drug products are not in the "effective" category.

instances where a drug in the "effective" category makes claims for uses as to which it may not be effective).

A great many of these products fall in the suspect categories because the data existing to support their claims of effectiveness do not meet the congressional standard of "substantial evidence" of effectiveness, since they are not based on adequate and well-controlled clinical investigations. Accordingly, in order to make manageable the responsibility imposed by Congress to withdraw approval of drugs lacking substantial evidence of effectiveness and still meet its obligation to hold hearings when substantial factual issues exist, FDA adopted the regulations at issue here. These regulations carefully define what constitutes "adequate and well-controlled investigations" (21 C.F.R. 130.12(a)(5)) and require the manufacturer seeking a hearing on effectiveness to submit studies apparently meeting these standards, failing which an order of withdrawal may be entered without a hearing (21 C.F.R. 130.14). The latter provision has been approvingly described as a "threshhold requirement" (*American Cyanamid Co.* v. *Richardson*, 456 F. 2d 509, 513 (C.A. 1)), and as a duty to present "the evidence needed to make out a *prima facie* case" (*Ciba-Geigy Corp.* v. *Richardson*, 446 F. 2d 466, 468 (C.A. 2)); it means no more than that a hearing would be a time-consuming and useless formality unless the manufacturer is prepared to present evidence of the precise type that Congress has required to support a decision in its favor.

The decision of the court of appeals in the instant case, while purporting to accept the validity of FDA's regulations and merely to reject the application of the regulations in this case, in reality rejects the entire purpose and utility of the regulations by imposing a standard that would necessitate a hearing in nearly every case. Hynson here sought to prove effectiveness through evidence the great majority of which consisted of medical opinion based upon experience and observation. However impressive such evidence may appear to laymen, this is precisely the type of proof Congress rejected as a basis for a showing of efficacy. Hynson did offer a few published and unpublished studies, but the NAS–NRC had little difficulty concluding that they did not meet the medical community's standards of adequacy (JA I, 7–8), and the Commissioner specifically identified how each fell short of compliance with the standards of 21 C.F.R. 130.12 (App. C, *infra*, pp. 17a–20a).

If the regulations are valid, therefore, the only issue that was before the court was whether the Commissioner's specific findings that Hynson had failed to meet the criteria for "adequate and well-controlled investigations" constituted a reasonable and adequately supported determination.[7] Instead, the court

[7] A recent decision of the court of appeals for the District of Columbia Circuit, *USV Pharmaceutical Corp.* v. *Secretary of Health, Education, and Welfare*, No. 24,900, decided August 14, 1972, set aside an order withdrawing approval of a drug without a hearing in a case which held that the Commissioner had failed at any stage of the proceeding to "present anything approaching a prima facie showing that there was no genuine and substantial issue of fact requiring a hearing" (slip op.,

found that the issue of effectiveness was raised sufficiently to warrant a hearing by such factors as (1) the absence of expert opinion that Lutrexin is ineffective, (2) the NAS–NRC conclusion that it was "possibly effective," (3) its safety, (4) the opinion of a former FDA employee that the studies of Lutrexin represented " 'well-controlled' clinical studies," and (5) the possibility that, after further inquiry at a hearing, it would turn out that the studies, notwithstanding their facial defects, would qualify under the regulations (App. A, *infra*, pp. 9a–11a).

The first three of these considerations clearly provide no support for the court's decision, since the statute imposes no burden on FDA to prove a drug ineffective and these considerations do not in any way indicate the existence of "substantial evidence" of effectiveness. The conclusions of the former FDA medical officer, while relevant, are immaterial because they fail to indicate any specific alleged error in the carefully detailed conclusions of the Commissioner

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p. 12). In the course of its opinion, the court indicated that, before requiring the manufacturer to submit material in support of a right to a hearing, the Commissioner was obliged to make a *prima facie* showing of facts and reasons leading to the conclusion that there was no genuine issue requiring a hearing. The court analogized the situation to the requirement imposed upon the movant for summary judgment in a civil suit.

This position, in our view, wrongly shifts the burden of producing evidence of effectiveness away from the applicant, where Congress intended it to be. In any event, the Commissioner's withdrawal order here contained a thorough and reasoned evaluation of the materials submitted in support of Hynson's claims of efficacy and correctly held them to be insufficient to raise a material issue of fact.

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regarding the adequacy of the studies.[8] As to the final consideration, it is of course always possible that a hearing would produce new information justifying a different conclusion about a given question, but surely neither the statute nor the regulations require the Commissioner to hold a hearing on the basis of such speculative possibilities. Instead, the statute and regulations are designed to accomplish expeditious removal from the market of drugs that are not of proven effectiveness. And sponsors of such drugs who, like Hynson, have failed to come forward with the kind of proof of effectiveness Congress has required are, of course, free in the future to submit new studies of efficacy in support of another new drug application for the same product.

It is thus apparent that the decision below is antithetical to the statutory policy and, in effect, invalidates the Commissioner's regulations implementing that policy. The evidence on which the court here relied is precisely the type of evidence Congress rejected as unreliable for purposes of the 1962 amendments. It is a type of evidence that very likely can be produced by the manufacturer in virtually every withdrawal proceeding. If the agency is to be compelled to conduct a full evidentiary hearing in every case where this type of proof is offered, it is difficult to see how

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[8] The witness, who was by then an officer of a major drug manufacturer, gave his affidavit in January 1970 (JAI, 76–77). His original views as to what constitutes adequate and well-controlled studies were published in 1964 (JAI, 86–94). The Commissioner's regulations defining the necessary content of such studies were promulgated on May 8, 1970.

or when it will be able to complete its fundamental task under the 1962 amendments of removing from the market drugs of unproved effectiveness.[9]

The basic error of the court below, in our view, was its failure properly to relate the procedural requirements for an evidentiary hearing to the substantive standards for withdrawal. The procedural regulations at issue here are based on the well-established principle that, even under statutes requiring a hearing, Congress did not intend agencies "to waste time on applications that do not state a valid basis for a hearing." *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192, 205; *Federal Power Commission* v. *Texaco Inc.*, 377 U.S. 33, 39. No hearing need be afforded if no material issue of fact is in dispute.[10] Whether such an issue is present can be determined only by reference to the specific substantive standards governing the proceeding. Here, as previously discussed, the 1962 amendments to the Act declare in Section 505(e) that

[9] In marked contrast to the court below, the District Court for the District of Columbia recently ruled that FDA has moved too slowly in discharging its responsibility to review the efficacy of drugs that had been approved for marketing prior to the 1962 amendments. *American Public Health Ass'n* v. *Veneman*, Civ. Action No. 1847–70, decided August 23, 1972. Manifestly, the agency will be unable to satisfy the thrust of that decision to expedite review and appropriate withdrawal actions if it must meet the standard for granting evidentiary hearings prior to withdrawal that has been imposed by the court of appeals in the instant case.

[10] See, *e.g.*, *Municipal Light Boards* v. *Federal Power Commission*, 450 F. 2d 1341, 1345 (C.A.D.C.); *Citizens for Allegan County* v. *Federal Power Commission*, 414 F. 2d 1125, 1128 and n. 5 (C.A.D.C.); *Virginia Electric and Power Co.* v. *Federal Power Commission*, 351 F. 2d 408, 410 (C.A. 4).

approvals shall be withdrawn if there is "a lack of substantial evidence" of effectiveness, and they expressly define substantial evidence in Section 505 (d) to mean "adequate and well-controlled investigations, including clinical investigations, by experts * * * on the basis of which it could * * * be concluded by such experts that the drug will have the effect * * *" claimed for it. The substantive issue pertinent here, therefore, is whether the investigations are adequate to permit experts to conclude that the drug is effective. Accordingly, the procedural issue under the regulations is whether the data proffered by the applicant are sufficient to raise this specific question at all—and not, as the court of appeals would have it, merely whether there is, in a more general sense, a "genuine issue of fact on the effectiveness of Lutrexin" (App. A, *infra*, p. 11a). If it is patent that the studies proffered are not "adequate and well-controlled investigations," no amount of testimony or cross-examination can make up the deficiency. See *Upjohn Co.* v. *Finch, supra,* 422 F. 2d at 955.

2. The decision below is subject to two possible interpretations: (1) that the proffer by the manufacturer of respectable evidence of effectiveness, even if not consisting of "substantial evidence" in the form of "adequate and well-controlled investigations" as required by Section 505(d) and 21 C.F.R. 130.12, is sufficient to raise an issue of effectiveness requiring resolution through an evidentiary hearing; or (2) that even if FDA is justified in conditioning the right to such a hearing upon a showing of "substantial evidence" as defined by statute and regulation, the

threshold determination of whether such a showing has been made itself requires an evidentiary hearing. Under either view, the decision basically conflicts with the rulings in *Pfizer, Inc.* v. *Richardson*, 434 F. 2d 536 (C.A. 2), and *Upjohn Co.* v. *Finch*, 422 F. 2d 944 (C.A. 6). The decision also conflicts with the thorough and carefully reasoned opinion of the district court in *Pharmaceutical Mfrs. Ass'n* v. *Richardson*, 318 F. Supp. 301 (D. Del.), upholding the validity of the regulations at issue here.

In both *Upjohn* and *Pfizer*, the Commissioner had withdrawn approval for certain antibiotics without a hearing.[11] In each instance, the manufacturer had submitted a large quantity of material that it contended demonstrated the effectiveness of the product, both as a general proposition and under standards like those of 21 C.F.R. 130.12. In each instance, the court of appeals upheld the Commissioner's action, concluding that he could properly refuse a hearing, no matter how much other evidence of effectiveness was produced, in the absence of a *prima facie* showing of the existence of "adequate and well-controlled investigations" (434 F. 2d at 544–546; 422 F. 2d at 950–955), and upholding the Commissioner's threshold, non-hearing determination that the manufacturer had failed to show the existence of such investigations (434 F. 2d at 546–547; 422 F. 2d at 951). With respect to the latter question, Judge Friendly observed for the court in *Pfizer* that "such a determination is

[11] The antibiotics involved in *Upjohn* generated revenues of about $30 million annually and represented a substantial portion of the manufacturer's total sales.

peculiarly within the FDA's expertise and we would be reluctant to intrude into medical matters we do not truly understand * * *" (434 F. 2d at 546). In contrast to the court below, the court in *Pfizer* concluded that the specific deficiencies detailed in the Commissioner's order (comparable to those specified in the order here) showed "that the FDA had a reasonable basis for considering that Pfizer's submissions did not comply with the requirement of the statute and the Regulation" (*id.* at 547). This, we submit, is the standard the court in the instant case also should have applied.

The only difference between the instant case and *Pfizer* or *Upjohn* is that the latter involved antibiotics under Section 507 (21 U.S.C. 357) rather than new drugs under Section 505. This difference is immaterial, however, since the basic statutory and regulatory scheme with regard to both types of products involves the same withdrawal of approval for ineffectiveness and the same "substantial evidence" requirement. Indeed, the Second Circuit, in *Ciba-Geigy Corp.* v. *Richardson,* 446 F. 2d 466, subsequently upheld as "reasonable and salutary" (*id.* at 468) the preconditions to evidentiary hearing in new drug cases specified in the regulations at issue here.

The issues presented by the decision below are of great importance to the Food and Drug Administration and the drug industry, and of special importance to the American consumer, for whom Congress sought to assure the reliability and effectiveness of prescription drugs. At the very least, this decision creates

undesirable confusion concerning questions apparently settled by previous decisions of other courts of appeals. If it is permitted to stand, the efforts of the Commissioner of Food and Drugs to implement the efficacy provisions of the 1962 drug amendments with respect to drugs marketed prior to their adoption will be seriously impaired.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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SEPTEMBER 1972.

APPENDIX A

United States Court of Appeals for the Fourth Circuit

No. 71-1717

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, PETITIONER

v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, RESPONDENTS

On Petition to Review an Order of the Commissioner of Food and Drugs

Argued February 7, 1972. Decided May 24, 1972.

Before BUTZNER, RUSSELL AND FIELD, *Circuit Judges.*

Edward Brown Williams (Jan Edward Williams and Harter, Calhoun and Williams, Robert H. Patterson, Jr., and McGuire, Woods and Battle, and John Kyle Worley on brief) for Petitioner, and Gregory B. Hovendon, Attorney, Department of Justice, (Richard W. McLaren, Assistant Attorney General, and Peter Barton Hutt, Assistant General Counsel, Food, Drugs and Environmental Health Division, Eugene M. Pfeifer, Attorney, United States Department of Health, Education, and Welfare, on brief) for Respondents. Joel E. Hoffman (Robert L. Wald, Selma M. Levine, and Wald, Harkrader and Ross on brief) for Amicus Curiae.

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RUSSELL, *Circuit Judge:*

The appellant, a drug manufacturer, seeks review of a final order withdrawing marketing approval (NDA) of the drug Lutrexin by the Commissioner of Food and Drugs, Department of Health, Education and Welfare.[1] The appellant alleges error in such order of withdrawal (1) for failure to sustain its claim of exemption from withdrawal on account of lack of "substantial evidence" of effectiveness of its drug and, if this claim of exemption is overruled, (2) for denial of a hearing, as required under the applicable statute, on its showing of effectiveness. We reverse.

The appellant was granted an approved NDA for Lutrexin in 1952. At that time, the Food, Drug and Cosmetic Act of 1938 conditioned such grant on general recognition of safety of the drug approved. In 1962 the Act was amended to authorize withdrawal of an approved NDA for any drug for which the Commissioner "after due notice and opportunity for hearing", found there was "a lack of substantial evidence of effectiveness."[2] The term "substantial evidence" was defined in the Amendments as "consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[3] There was an exemption from these requirements for drugs, which, *inter alia,* were not

[1] Section 355(h), 21 U.S.C.
[2] Section 355(e), 21 U.S.C.
[3] Section 355(d), 21 U.S.C.

covered on the day immediately before the enacting date of the Amendments (i.e., October 9, 1962) by an "effective NDA".[4]

In carrying out his new responsibilities under the Amendments, the Commissioner secured the services of the National Academy of Sciences-National Research Council (NAS–NRC) for reviewing the claims of effectiveness on behalf of any drugs NDA'd between 1938 and 1962.[5] To facilitate its assignment, NAS–NRC set up a Drug Efficacy Study Group and all drug manufacturers with approved NDAs obtained between 1938 and 1962 were directed by the Commissioner to submit to this Group evidence "pertinent to the evaluation of the effectiveness of the(ir) drugs."[6] The appellant submitted to the Group clinical data, investigations and studies in support of the effectiveness for its drug Lutrexin. After considering such data, NAS–NRC concluded that Lutrexin was "possibly effective" but indicated the supporting documentation was inadequate.

The Commissioner advised the appellant of his concurrence with the conclusions of NAS–NRC and, as required by the statute, extended to it an opportunity for a hearing on the proposed withdrawal of the ap-

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[4] "In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force * * *, and (C) was not covered by an effective application under section 505 of that Act * * *, the amendments to section 201(p) * * * made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day." Section 107(c)(4), appended to Section 321, 21 U.S.C., 1972 Supplement, p. 192.

[5] 21 F.R. 13014, October 6, 1966.

[6] 21 F.R. 13014.

proved NDA for Lutrexin.[7] At such a hearing, the appellant was advised it might "produce evidence and arguments why approval * * * should not be withdrawn."[8] The appellant in due time requested such hearing. Under the Commissioner's regulations, a hearing was required within 90 days after such request, unless the parties agreed otherwise.[9] However, although no delay was agreed on, hearing within such period was not had. The delay on the part of the Commissioner in setting a hearing was due to litigation over the procedure to be followed by it in implementing its efficacy review and in conducting hearings resulting therefrom.[10] It is unnecessary to review the difficulties encountered in developing valid regulations for such hearings. It is sufficient for the issues here that it was not until May 8, 1970, that the legal objections to the regulations were finally resolved.

During this interregnum when the regulations of the Agency were under challenge and the Commissioner was delaying a hearing, the appellant, whose request for a hearing had been delayed for more than a year, sought in District Court a declaratory judgment to the effect that, under the exemption clause included in the 1962 Amendments, Lutrexin was not a "new drug" on and before October 10, 1962, and was thereby exempt from the requirement of evidence of effectiveness under the Amendments. Such action was dismissed on the ground that primary jurisdiction to resolve the issue of exemption under the Act rested with the Commissioner. No appeal was taken from this dismissal.

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[7] 33 F.R. 7701.

[8] 34 F.R. 5556.

[9] 21 C.F.R. 130.14(b).

[10] See *Pharmaceutical Manufacturers Association* v. *Finch* (D.C.Del. 1970) 307 F. Supp. 858; *Upjohn* v. *Finch* (6th Cir. 1970) 422 F. 2d 944; and *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536.

While this declaratory action was pending, the Commissioner issued his new regulations detailing the circumstances under which an applicant might secure a hearing on a proposal by the Commissioner for withdrawal of an effective NDA. By these regulations, the Commissioner was authorized to deny a hearing, "when it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data".[11]

After the regulation had been legally promulgated, which was more than a year after the appellant had requested a hearing, the Commissioner directed the appellant's attention to these new regulations and suggested that it amend its request for a hearing to comply. Though it contended it had, by its earlier request, perfected its right to a hearing and was not obligated to amend its request, the appellant did, following the dismissal of its declaratory action, submit a considerable amount of clinical medical studies and investigations in support of the claim of effectiveness for its product by way of compliance with the new regulations. The Commissioner, however, dismissed the appellant's request for a hearing on the basis of such showing, finding (1) that its drug was a "new drug" requiring proof of effectiveness, and (2) that its showing of effectiveness was insufficient to demonstrate a "genuine and material issue of fact" under the test of "substantial evidence" as defined in the Amendments.

[11] 21 C.F.R. 130.14(b).

On the basis of these findings it withdrew the approved NDA for Lutrexin. It is from this order that appeal has been taken.

I

The appellant's claim to an exemption for its drug is easily disposed of. We have held in a related case that a drug covered by a pre-1962 approved NDA, which had not been withdrawn under the procedure set forth in Section 505(e), is not entitled to the exemption granted under Section 107(c)(4) of the Amendments.[12] The appellant's NDA was outstanding and had not been legally withdrawn on October 10, 1962. It cannot accordingly claim the benefit of the exemption statute for its drug. While the appellant was entitled to have this issue resolved by the District Court, it was not prejudiced by, and cannot complain of, the refusal by the District Court to exercise jurisdiction. Nor, for that matter, did the appellant appeal and is accordingly without standing in this proceeding to challenge that dismissal.

II

The crucial issue in this case, however, is posed by the appellant's second contention and revolves about the requirement in the Act that, before the entry of a final order of withdrawal, the applicant be given an "opportunity for hearing". At such a hearing, the procedure adopted by the Commissioner allows the applicant to "produce evidence and arguments to show why approvals of (its drugs) * * * should not be withdrawn."[12a] Of course, the Commissioner might, as he

[12] *USV Pharmaceutical Corp.* v. *Richardson*, (4th Cir. 1972) ——— F. 2d ———.

[12a] Whether this is too narrow and improperly confines the scope of the hearing, so far as it is adjudicatory, see Davis, *The Requirement of a Trial-Type Hearing*, 70 Har. L. Rev. 193 (1956).

did by his regulations issued in 1970, provide for the denial of a hearing where it clearly appeared from the applicant's own showing there was no "genuine and substantial issue of fact" on which the claim of the applicant might be sustained. *Ciba-Geigy Corp.* v. *Richardson* (2d Cir. 1971) 446 F. 2d 466, 468. It may be assumed that such regulation, when issued will apply to all pending applications. *U.S.* v. *Storer Broadcasting Co.* (1956) 351 U.S. 192, 205. But, in applying this regulation and in making his determination thereunder, the Commissioner's discretion is not absolute. Neither due process nor the Administrative Practice Act permits an arbitrary denial in any case where it can be fairly said there are "genuine and substantial issues of fact" in dispute.[13]

Such a denial would, in addition, be violative of the Congressional purpose expressed in the provision for a hearing. And the courts must see that such Congressional purpose is not thwarted by administrative usurpation; or, as the Court said in *Environmental Defense Fund, Inc.* v. *Ruckelshaus* (D.C.C.A. 1971) 439 F. 2d 584, 596, the courts have "an obligation to ensure that the administrative standards conform to the legislative purpose * * *." Accordingly, only if

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[13] See *Ciba-Geigy Corp.* v. *Richardson*, *supra*, at p. 468. The question is analogous to that presented by a demand for a hearing in connection with an N.L.R.B. election where the right to a hearing subject to the same general limitations as stated in the Commissioner's regulations, and it would seem the same test of the right to a hearing is applicable. For the rule in such N.L.R.B. case, see *N.L.R.B.* v. *Bata Shoe Co.* (4th Cir. 1967) 377 F. 2d 821, 825–6; *United States Rubber Co.* v. *N.L.R.B.* (5th Cir. 1967) 373 F. 2d 602, 606; *N.L.R.B.* v. *Smith Industries, Inc.* (5th Cir. 1968) 403 F. 2d 889, 892–5.

it can be fairly said that the clinical tests and medical studies and investigations submitted by the applicant, if credited and accepted, will not support a finding that they provide "substantial evidence" of effectiveness was it proper for the Commissioner to deny the appellant a hearing *before* entering a final order of withdrawal. The judicial test is somewhat the converse of that to be applied in a review of a decision of the Commissioner entered *after* a hearing. In that instance, his decision is to be upheld, if sustained by any substantial evidence.[14] But in determining whether the Commissioner acted within the limits of his discretion on the procedural question of whether a hearing is to be allowed, the test is whether there is any "genuine and substantial" evidence that supports the position of the applicant.

Manifestly, the applicant does not have to satisfy or convince the Commissioner by his evidence that his product is effective as a predicate for securing his right to a hearing. If that was his burden, a hearing would never be necessary or appropriate. If he, by his showing, convinced or satisfied the Commissioner, the proposed withdrawal would naturally be denied; on the other hand, if he failed to satisfy, then the Commissioner would deny a hearing and order withdrawal. In either event, a hearing would be useless and the Congressional promise of a hearing would be purely illusory. No such exacting standard of proof is required as a basis simply for the right to be heard; as has been observed, all that is required for securing a right to a hearing is that the showing be such that, if accepted, a finding of "substantial evidence" of effectiveness would be supportable. And "substantial" in this connection does not mean "preponderant evidence" or "conclusive evidence". Congress specifically

[14] Section 355(h), 21 U.S.C.

discarded those terms for the milder term "substantial," which was understood to embrace the idea, not of a preponderance but rather of a responsible body of qualified opinion."

Applying the foregoing principles, we are of opinion the showing of the appellant was such that, under a reasonable construction of the Commissioner's own regulations, as well as under familiar principles of due process, and the requirements of the Administrative Procedure Act, it was entitled to an impartial hearing before its NDA was withdrawn. It must be noted that no qualified expert has given an opinion that Lutrexin is ineffective for the uses in-

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"In the course of committee deliberation a distinction evolved * * * between two tests the "preponderant evidence" test and the "substantial evidence" test as now specifically defined. Under the former a claim would not be accepted under the new drug section unless it represented the preponderant view of experts * * * the committee recognizes that in the difficult area of drug testing and evaluation there will frequently, if not usually, be a difference of responsible opinion. The committee feels the existence of such a difference should not result in disapproval of a claim of effectiveness if it is supported by substantial evidence defined in the manner set forth below [that is adequate and well controlled investigations by qualified experts upon the basis of which conclusions made be fairly and responsibly drawn.].

[Application of the substantial evidence test means that] a claim could be rejected if it were found (a) that the investigations were not "adequate"; (b) that they were not "well-controlled"; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which its application is made; or (d) that the conclusions to be drawn by such experts could not fairly and responsibly be derived from their investigation.

S. Rep. No. 1744, 87th Cong., 2nd Sess. Part II, pp. 5–6, and see, 2 U.S. Code Congress. & Administrative News, 87th Cong., 2d Sess., p. 2892 (1962).

tended. The NAS–NRC review concluded it was "possibly effective". Neither is there any contention that it is unsafe when used for the purposes intended. The real basis for the determination by the Commissioner that the appellant had failed to make a showing of any genuine issue of fact on the effectiveness of its drug was the conclusion that the various scientific articles and tests submitted by the appellant were not "adequate and well-controlled clinical investigations" within the statutory definition of "substantial evidence". In his decision, the Commissioner sought to point out the deficiencies in the investigations submitted by the appellant which justified this conclusion. In so doing, he did not impugn the competency or qualifications of the scientists and medical experts whose investigations were cited by the appellant in support of its claim. Their professional qualifications, as they appear in the record, are impressive. Their investigations and opinions, some of which have been published in recognized professional medical journals, are, however, dismissed by the Commissioner with the statement that, "No adequate and well-controlled clinical investigations published in the medical literature had been identified."

In making that statement, he disregards the categorical opinion of his former Director of the Bureau of Medicine and Medical Director that the clinical tests and investigations submitted by the appellant represented "'well-controlled' clinical studies". He proceeds to fault two investigations published in an authoritative medical journal, submitted by the appellant, because, "There is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced", and "There is no summary or explanation of the statistical methods used in analysis of the data to show that results were not biased or due to chance".

Another unpublished investigation is dismissed because, "Substantiating documentation to establish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided". Two published studies by a clinical professor of Obstetrics at the University of Illinois are criticized, in one instance, because "The report does not state the method of patient selection" and "Concomitant medication is not excluded" and, in the other, because "The method of selection of the patients does not show progressive dilation of the cervix, which is necessary to accurately diagnose premature labor."

Assuming that all the objections by the Commissioner to these clinical studies, conducted as they were by competent medical authorities, may have some validity, they do not justify a final conclusion, made *ex parte,* without a hearing, that it "clearly appears" that there is no genuine issue of fact on the effectiveness of Lutrexin, which is the test under the Commissioner's own regulation for denial of a hearing; at most, they merely create a genuine question of fact to be resolved at a hearing upon proper evidence. Whether the studies were as controlled as they might have been and whether there was a failure in these studies as published to fill in all the details the Commissioner might think appropriate are matters that could be developed at a hearing, after the authors were examined and the reliability of the investigations further inquired into.

The order of the Commissioner, from which this appeal is taken, is set aside for failure to provide the petitioner with an "opportunity for a hearing" before the entry of said order.

Reversed.

APPENDIX B

United States Court of Appeals for the Fourth Circuit

No. 71-1717

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, PETITIONER

v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION, WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, RESPONDENTS

On Petition to Review an Order of the Commissioner of Food and Drugs

THIS CAUSE came on to be heard upon the petition of Hynson, Westcott and Dunning, Incorporated, for review of an order issued against it by Elliot Richardson, Secretary of Health, Education, Welfare, and Charles C. Edwards, Commissioner of Food and Drugs, on May 31, 1971, in proceedings before the said Agency; and upon a certified list in lieu of a transcript of the record; and the said cause was argued by counsel.

ON CONSIDERATION WHEREOF, it is ordered, adjudged and decreed by the United States Court of Appeals for the Fourth Circuit, that the order of the Commissioner, from which this appeal is taken, is set aside for failure to provide the petitioner with an "opportunity for a hearing" before the entry of said order. The order is reversed.

A True Copy, Teste:
Filed May 24, 1972.

SAMUEL W. PHILLIPS,
Clerk.

By J. U. LAYARD,
Deputy Clerk.

APPENDIX C

[Docket No. FDC–D–123; NDA No. 8–986 and 10–144]

HYNSON, WESTCOTT & DUNNING, INC.

Notice of Withdrawal of Approval of New-Drug Applications

On March 22, 1969, there was published in the Federal Register (34 F.R. 5556) a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new-drug applications for drugs containing lututrin on the ground that there is a lack of substantial evidence that lututrin has the effect or contributes to the effect which the drugs purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Hynson, Westcott & Dunning, Inc., Charles and Chase Streets, Baltimore, Md. 21201, holder of NDA No. 8–986, Lutrexin tablets and NDA No. 10–144, Trexinest tablets by the October 16, 1970 letter of its counsel, has requested a hearing on the following issues:

(1) Whether its lututrin drugs are exempt from the efficacy requirements of 21 U.S.C. 355 under section 107(c) of Public Law 87–781; (2) whether its lututrin drugs are "new drugs" within the meaning of 21 U.S.C. 321(p)(1); and (3) whether there is a lack of substantial evidence of effectiveness to support the claims made for Lutrexin.

In support of its request for a hearing on the issue of substantial evidence of effectiveness, Hynson, Westcott, and Dunning, Inc. (hereinafter referred to as "HW&D") has submitted a list of its medical documentation previously filed with the Agency, including all data submitted in connection with NDA No. 10-144, correspondence between HW&D officials and the Agency or other persons, labeling for the lututrin drugs, literature articles submitted to the National Academy of Science-National Research Council, and the HW&D letter of August 18, 1969, in which the company first elected to avail itself of the opportunity for hearing.

To support its hearing request on the contentions that HW&D's lututrin drugs are exempt from the efficacy requirements of 21 U.S.C. 355, the company has submitted copies of its pleadings, legal memorandum, exhibits, and affidavits, as well as the transcript and order in Hynson, Westcott and Dunning, Inc., v. Finch (C.A. No. 21112, D. Md., decided Sept 11, 1970).

The Commissioner of Food and Drugs has reviewed HW&D's request for hearing and the medical documentation submitted, and makes the following findings:

I. *The drugs, their rationale and claims.* a. Lutrexin is labeled as containing 3,000 units of lututrin per tablet. Lututrin is claimed to be a pig uterine relaxing hormone effective in the treatment of functional dysmerorrhea, selected cases of premature labor and threatened and habitual abortion. The package insert claims the drug has demonstrated activity on the living animal uterus, that it relaxes the contracted uterine muscle by direct action thereon, or by blocking pituitary action.

b. Trexinest is labeled as containing 500 units of lututrin and 1.0 milligrams of estrogen, in the form of sodium estrone sulfate, per tablet. Trexinest is recommended for the treatment of menopausal disorders. The package insert claims that the combination is more effective than lututrin or estrogen alone and points to lututrin as the responsible agent in the drug's effectiveness.

II. *The applicable regulations.* HW&D's contention that it has an unconditional right to a hearing is denied. The hearing regulations, 21 CFR 130.14, require that a person seeking a hearing set forth specific facts showing the existence of genuine and substantial fact issues which requires a hearing. The order of May 8, 1970 (35 F.R. 7250) granted persons involved in notices of hearing, including HW&D, 30 days in which to amend their requests for hearing to comply with the new regulations. The company was given actual notice on May 19, 1970, that it was required to comply with these regulations in order to properly avail itself of an opportunity for hearing. Applications of the regulations have been upheld by the courts. Pfizer, Inc. v. Richardson, 434 F. 2d 536 (C.A. 2, 1970); Upjohn Co. v. Finch, 422 F. 2d 944 (C.A. 6, 1970); Pharmaceutical Manufacturers Association v. Richardson, 318 F. Supp. 301 (D. Del., 1970). HW&D is bound by the judgment in the last case cited.

III. *The Request for a Hearing*—a. *The issues of exemption under section 107(c) of Public Law 87-781 and under 21 U.S.C. 321 (p)(1).* The request for a hearing on these issues is denied. The new-drug applications involved had not been withdrawn prior to enactment of Public Law 87-781. They were "deemed approved" under the 1962 amendments to the Act and are subject to withdrawal on the basis of the effectiveness requirements of the amendments.

b. *Lutrexin and Trexinest are new drugs within the meaning of 21 U.S.C. 321 (p)(1).* The conclusions of HW&D's affiants that these drugs are not new drugs cannot be accepted. No adequate and well-controlled clinical investigations published in the medical literature have been identified. Therefore, there is no data base upon which experts can fairly and responsibly conclude that the safety and effectiveness of the drugs has been proven and is so well established that the drugs can be generally recognized among such experts as safe and effective for their intended uses.

The affiants identify 11 studies as establishing the claims made for the drugs. None purports to be an adequate and well-controlled clinical investigation. They may be summarized as follows:

(1) Majewski and Jennings: Uterine Relaxing Factor for Premature Labor, Ob. & Gyn. 5:649–652 (May 1955); and Further Experiences with a Uterine Relaxing Hormone in Premature Labor, Ob. & Gyn. 9:322–325 (March 1957) by the same authors are one study. The first paper is a preliminary study on 20 patients and the latter is the report on enlarged group of 88 patients. The authors acknowledge that results in the total group are less favorable than in the preliminary study, but conclude that the results are encouraging. Concomitant medication was given an unstated number of patients. There is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced. Nine patients out of 88 in whom the drug proved ineffective were excluded from the report for "statistical reasons". Six patients received the drug for less than 3 hours, which the authors without explanation considered too short a time for a true test of effectiveness. There is no summary or explanation of the statistical methods used in analysis of the data to show that results were not biased or due to chance.

(2) Majewski: Statistical Evaluation in The Reduction of the Incidence of Prematurity (1968) is unpublished. The author claims successful treatment in 86 percent of cases treated in his practice over a 10-year period. Substantiating documentation to establish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided. The author acknowledges that some patients with medical complications such as placenta praevia were included in the study. Lutrexin is not claimed to have value in the medical or obstetrical complications of pregnancy which occur in a significant percentage of premature births.

The paring of live birth percentages by number of pregnancies before and after Lutrexin treatment such as in Table I are all inappropriate. For example, of the 24 cases with one previous pregnancy, 11 live births before treatment and 18 live births after treatment are compared. However, for each of the 18 live births after treatment, an additional pregnancy had elapsed so that the number of previous pregnancies associated with the number 18 is two, not one; as such, the number 18 should be compared with the number 16, the total live births for two previous pregnancies.

The data in Table I does not admit of statistical evaluation by the chi-square test since the test is based on the assumption that each number in the columns of Table I is the sum of independent yes or no responses, e.g., for the one patient with seven previous pregnancies, four live births are correlated, thus ignoring the sample size of one and using an erroneous sample size of four.

(3) Rezek: The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luterum in the Treatment of Dysmenorrhea, Am. J. Ob. & Gyn. 66:396-402 (August 1953). The report does not state the method

of patient selection, nor does it indicate comparability of pertinent variables such as severity or duration of diseases. Concomitant medication is not excluded. No explanations of the methods of observation, the recording of results, and steps taken to minimize patient and investigator bias are provided. The historical controls employed are inappropriate.

(4) Rezek: Lutrexin in the Treatment of Premature Labor, Ann. N.Y. Acad. Sci. 75:995–997 (January 1959). The method if selection of the patients does not show progressive dilation of the cervix, which is necessary to accurately diagnose premature labor. The methods of observation and the recording of results are not explained. No statistical evaluation was presented to show that results claimed are significant in terms of the patient population.

(5) Gratton: The Treatment of Infertility and Prematurity Pregnancy Problems (1968) is unpublished. Patients received numerous concomitant therapies until the fifth month of pregnancy which prevents scientific attribution of results of lututrin therapy. The method of patient selection is unexplained.

Statistically the study lacks adequate design and evaluation. There is no showing that the cases studied are representative of the population to which inferences are made. The pairings of live births percentages in Table II cannot be compared since the number of previous pregnancies differs between the pair percentages and there is no data on possible etiologic factors of previous abortions and premature labor.

(6) Gray: Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases (undated) is an unpublished report on 15 selected cases the author has treated. No plan or protocol is provided to allow deter-

mination of the objectives of the study, the method of patient selection, diagnostic criteria of the condition to be treated, laboratory tests to be made, the methods of observation and recording of results. The author's review of his records does not constitute an adequate and well-controlled investigation.

(7) Four papers by Dr. Trythall were listed in the attachment to his affidavit. In only one article is Lutrexin ever mentioned. The three sentences devoted to the drug provide no information whatsoever except that the author claims to have found it effective in his practice.

The affiants state that double blind investigations of lututrin are unethical because the drug is effective and complications of pregnancy may be life-threatening. The Commissioner does not reach that issue, since none of the historically controlled studies relied upon were adequate and well-controlled investigations.

There are other reasons why HW&D's medical data lack merit, but in view of the above finding their delineation is unnecessary.

c. *The issue of substantial evidence of effectiveness.* The request for a hearing on this ground is denied. The regulations, 21 CFR 130.14, require HW&D to submit a well organized and full factual analysis of the clinical and other investigational data it is prepared to prove at a hearing. The request must set forth specific facts showing that there is a genuine and substantial issue of fact requiring a hearing. HW&D has not attempted compliance with these requirements.

Rather than identify and discuss the efficacy data relied upon to support the claims made for its drugs, the company has merely provided a list, extending to four pages, of practically all materials ever submitted to the Agency and the NAS–NRC. The materials are described, for the most part, in general terms (e.g.,

"data submitted in connection with New Drug Application for Lutrexin tablets * * *, Lutrexin bibliography * * *, Trexinest bibliography * * *, reprints and abstracts * * *). What the Commissioner is required to do is determine from this material, what HW&D may or may not consider relevant and, therefore, relies upon. In the case bibliographies, the Commissioner would be required to research each article and then determine if it is relevant, or whether HW&D might consider it relevant. Because such a procedure is not contemplated by the regulation, the request for hearing is denied for failure to comply with applicable regulations.

Apart from the refusal of HW&D to comply with 21 CFR 130.14, the most basic material in the Lutrexin new-drug application reveals a lack of adequate and well-controlled investigations showing that lututrin will have the effect HW&D claims for it.

The only evidence submitted that lututrin may have biological activity in humans when taken orally is a test on nine women by Jones and Smith in which positive results were reported to have been obtained in six subjects. No plan or protocol was stated. No data on the participating patients was provided. No explanation of procedures for patient selection, or criteria for inclusion in the study, or appropriate laboratory tests before and after administration of lututrin was provided. No statistical analysis showing the test population was of significant size or that results obtained were significant is shown. Moreover, there is no evidence that results claimed have ever been reproduced in humans by other investigators.

Therefore, the Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1053, as amended; 21 U.S.C. 355(e)), and under the authority

delegated to him (21 CFR 2.120), finds that on the basis of new information before him with respect to each of said drugs, evaluated together with the evidence available to him when each application was approved, there is a lack of substantial evidence that each of the drugs will have the effects it is purported or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof.

Pursuant to the foregoing findings, approvals of the above new-drug applications, and all amendments and supplements thereto, are withdrawn effective on the date of the signature of this document.

Dated: May 31, 1971.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[F.R. Doc. 71-8557 Filed 6-17-71; 8:46 a.m.]

APPENDIX D

21 C.F.R. 130.12(a)(5) as amended, 35 F.R. 7251, May 8, 1970, provides:

> (a) If the Commissioner determines upon the basis of the application, or upon the basis of other information before him with respect to the new drug, that * * *
>
> (5)(i) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.
>
> (ii) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is "substantial evidence" to support the claims of effectiveness for "new drugs" and antibiotic drugs.
>
> (*a*) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:
>
> (1) A clear statement of the objectives of the study.

(2) A method of selection of the subjects that—

(*i*) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired.

(*ii*) Assigns the subjects to test groups in such a way as to minimize bias.

(*iii*) Assures comparability in test and control groups of pertinent variables, such as age, sex, severity, or duration of disease, and use of drugs other than the test drug.

(3) Explains the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subjective response, and steps taken to minimize bias on the part of the subject and observer.

(4) Provides a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. Level and methods of "blinding," if used, are to be documented. Generally, four types of comparison are recognized:

(i) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients.

(ii) Placebo control: Comparison of the results of use of the new drug entity with an inactive preparation designed to resemble the test drug as far as possible.

(*iii*) Active treatment control: An effective regimen of therapy may be used for comparison, e.g., where the condition treated is such that no treatment or administration of a placebo would be contrary to the interest of the patient.

(*iv*) Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen (therapeutic, diagnostic, prophylactic) the effectiveness of which is established.

(5) A summary of the methods of analysis, and an evaluation of data derived from the study, including any appropriate statistical methods.

Provided, however, That any of the above criteria may be waived in whole or in part, either prior to the investigation or in the evaluation of a completed study, by the Director of the Bureau of Drugs with respect to a specific clinical investigation; a petition for such a waiver may be filed by any person who would be adversely affected by the application of the criteria to a particular clinical investigation; the petition should show that some or all of the criteria are not reasonably applicable to the investigation and that alternative procedures can be, or have been, followed, the results of which will or have yielded data that can and should be accepted as substantial evidence of the drug's effectiveness. A petition for a waiver

shall set forth clearly and concisely the specific provision or provisions in the criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been, employed, what results have been obtained, and the basis on which it can be, or has been, concluded that the clinical investigation will or has yielded substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(*b*) For such an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(*c*) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

(6) Based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; the Commissioner shall within 180 days after the filing of the application inform the applicant in writing of his intention to issue a notice of hearing on a proposal to refuse to approve the application.

(b) Unless by the 30th day following the date of issuance of the letter informing the appli-

cant of the intention to issue a notice of hearing, the applicant:

(1) Withdraws the application; or

(2) Waives the opportunity for a hearing; or

(3) Agrees with the Commissioner on an additional period to precede issuance of such notice of hearing,

the Commissioner shall expeditiously notify the applicant of an opportunity for a hearing on the question of whether such application is approvable as provided in § 130.14.

21 C.F.R. 130.14, as amended, 35 F.R. 7252, May 6, 1970, provides:

(a) The notice to the applicant of opportunity for a hearing on a proposal by the Commissioner to refuse to approve an application or to withdraw the approval of an application will specify the grounds upon which he proposes to issue an order. On request of the applicant, the Commissioner will explain the reasons for his action. The notice of hearing will be published in the Federal Register and will specify that the applicant has 30 days after issuance of the notice within which he is required to file a written appearance electing whether:

(1) To avail himself of the opportunity for a hearing at the place specified in the notice of hearing; or

(2) Not to avail himself of the opportunity for a hearing.

(b) If the applicant elects to avail himself of the opportunity for a hearing, he is required to file a written appearance requesting the hearing within 30 days after the publication of the notice and giving the reason why the application should not be refused or should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition to the notice of opportunity

for a hearing. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data. If a hearing is requested and is justified by the applicant's response to the notice of hearing, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence, not more than 90 days after the expiration of such 30 days unless the hearing examiner and the applicant otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval.

(c) The hearing will be open to the public: *Provided, however,* That if the Commissioner finds that portions of the application which serve as a basis for the hearing contain information concerning a method or process which as a trade secret is entitled to protection, the part of the hearing that involves such portions will not be public unless the respondent so specifies in his appearance.

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-414

HYMAN, WEITZOFF & DUBBINS, INCORPORATED,
Cross-petitioner,
v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS,
Respondents.

CROSS-PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

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IN THE

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HYNSON, WESTCOTT & DUNNING, INCORPORATED,
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v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH EDUCATION AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS,
Respondents.

CROSS-PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

Cross-Petitioner, Hynson, Westcott & Dunning, Incorporated, respectfully prays that a writ of certiorari issue to review in part the judgment and opinion of the United States Court of Appeals for the Fourth Circuit entered in this proceeding on May 24, 1972.

OPINIONS BELOW

The opinion of the Court of Appeals and its opinion in two related cases, none of which has yet been officially reported, appear in Appendices A, B, and C, *infra*. The Order of the Commissioner of Food and Drugs also appears in Appendix A.[1]

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[1] The Appendices are cited hereafter as "App." They are to be distinguished from Volumes I & II of the Joint Appendix filed below ("Jt. App. I & II").

JURISDICTION

The judgment of the United States Court of Appeals for the Fourth Circuit was entered May 24, 1972. The jurisdiction of this Court is invoked under 28 U.S.C. Section 1254(1).

EXTENSION OF TIME

By order of August 17, 1972, Mr. Justice Rehnquist extended the time within which to file a petition for a writ of certiorari in this matter (No. A-205) to and including September 11, 1972.

STATUTES INVOLVED

The pertinent statutory provisions, which are set forth in Appendix A, *infra*, are (1) the following sections of the Federal Food, Drug and Cosmetic Act, 52 Stat. 1040, as amended, 21 U.S.C. 301, et seq: Sections 201 (p), 21 U.S.C. 321(p), 502(a), 21 U.S.C. 352(a) and 505, 21 U.S.C. 355, and (2) Section 107 of the Drug Amendments of 1962, P.L. 87-781.

QUESTIONS PRESENTED

The Federal Food, Drug and Cosmetic Act requires manufacturers of "new drugs" as therein defined (Section 201(p)) to obtain pre-marketing approvals of new drug applications for such drugs.

The Act, as amended by the Drug Amendments of 1962, provides for administrative withdrawal-of-approval of a new drug application on the ground that there is a lack of substantial evidence of effectiveness of the subject drug (Section 505(e)(3)). Only drugs "deemed approved" under the amendments (Section 107 (c)(2)) are subject to such administrative withdrawal proceedings. The 1962 Amendments also exempt cer-

tain drugs from all effectiveness provisions and hence from their enforcement either administratively or judicially (Section 107(c)(4) of the amendments). The Food and Drug Administration decided, without a hearing, that cross-petitioner's drug, Lutrexin, is a "new drug," that there is a lack of substantial evidence of its effectiveness, that it was "deemed approved", and that it was not exempt under Section 107(c)(4) of the 1962 amendments.

The Questions presented are:

(1) Whether, in a proceeding to withdraw approval of a new drug application, the Commissioner of Food and Drugs is without authority to determine initially his own jurisdiction to conduct such a proceeding.

(2) Whether one whose drug is subjected to such a withdrawal proceeding is entitled to an administrative hearing at which evidence may be introduced as a basis for deciding whether the Commissioner has jurisdiction to conduct such a proceeding.

(3) Whether a new drug application for a drug which had become generally recognized as safe the day before the effective date of the Drug Amendments of 1962 (October 9, 1962) was no longer an "effective" application within the meaning of Section 107(c)(2) of such amendments and therefore such application was not "deemed approved" under that section.

(4) Whether a drug which had become generally recognized as safe on the day before the effective date of the Drug Amendments of 1962 was a "new drug" on that date and was "covered by an effective application" within the meaning of Section 107(c)(4)(B) and (C) of such Amendments.

STATEMENT

Cross-petitioner, Hynson, Westcott & Dunning, Incorporated (HW&D), sought review in the Court of Appeals for the Fourth Circuit, of an order of the Commissioner of Food and Drugs, published in the Federal Register of June 18, 1971 (36 F.R. 11763, App. B(1), 10a), withdrawing approval of the new drug application (NDA) for HW&D's drugs, Lutrexin and Trexinest.[2] Direct appeal to the Court of Appeals is authorized by Section 505(h), 21 U.S.C. 355(h), of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 301 et seq., the "Act").[3] Under the Act, a "new drug", as therein defined (Section 201(p), 21 U.S.C. 321(p)), cannot be marketed without an approved new drug application.[4]

The Court of Appeals set aside the order of the Commissioner on the ground that HW&D was entitled to a hearing, which had been denied by the Commissioner, on the question of whether approval of HW&D's NDA should be withdrawn under Section 505(e)(3) of the Act, 21 U.S.C. 355(e)(3), as amended in 1962, because there is a lack of substantial evidence of effectiveness of Lutrexin. This cross-petition is filed because, as hereinafter set forth in more detail, the Court (a) decided erroneously that, at the required hearing the Food and Drug Administration (FDA) was without authority to determine its own jurisdiction, (b) decided erroneously one jurisdictional question before it—whether Lutrexin was exempt from the effectiveness requirements of the

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[2] The marketing of Trexinest has been discontinued by HW&D. This case is not concerned with that drug.

[3] Section 505(h) is set forth in Appendix A at 6a.

[4] Marketing of a new drug without an NDA is prohibited by Section 301(d) and 505(a) of the Act, 21 U.S.C. 331(d) and 355(a), under sanction of injunctive, criminal proceedings, or seizure (Sections 302, 303, and 304, 21 U.S.C. 332, 333, and 334).

Drug Amendments of 1962[5] by Section 107(c)(4) of those amendments, (c) failed to deal with the jurisdictional question of whether Lutrexin was exempt from withdrawal-of-approval proceedings under Section 505 (e)(3) of the Act by Section 107(c)(2) of the amendments, and (d) failed to deal with the matter of HW&D's right to a hearing on the two jurisdictional questions above stated and the additional one of whether Lutrexin is now generally recognized as both safe and effective, and, therefore, not a new drug subject to the new-drug provisions of the Act.

HW&D has since 1953 marketed Lutrexin, a prescription drug, for use in the treatment of premature labor, second and third trimester threatened abortion, and dysmenorrhea (menstrual discomfort). The drug was, when first marketed in 1953, a "new drug" within the meaning of Section 201(p) of the Federal Food, Drug and Cosmetic Act as then written. Pre-marketing clearance of Lutrexin under the new drug provisions of Section 505 of the Act was, therefore, necessary, and a new drug application for the drug was filed and became effective on December 23, 1953.

Until 1962 the test under Section 201(p) for determining the necessity for obtaining pre-marketing clearance of a drug was whether the product was generally recognized as safe by qualified experts. Congress, in the Drug Amendments of 1962, amended Sections 201(p) and 505 of the Act to require pre-market clearance of new drugs for both safety and effectiveness. Thus, Section 201(p), as amended, defined "new drugs" as those not generally recognized by qualified experts as both safe *and* effective for their intended uses.

Congress also added to Section 505(d) and (e) the concept of "substantial evidence of effectiveness," a con-

[5] P.L. 87-781.

cept separate and apart from the concept of general recognition of safety and effectiveness. The latter is solely a jurisdictional test. The manufacturer of a product which was a new drug because of a lack of general recognition of effectiveness would, under amended Section 505, in order to obtain approval of an NDA for his product, have to supply FDA with substantial evidence of the effectiveness of the drug. Likewise, where appropriate, FDA could, under Section 505(e)(3), withdraw approval of a new drug's NDA if it found a lack of substantial evidence of the drug's effectiveness.

The Court of Appeals held that HW&D was entitled to a hearing on the question of whether there is a lack of substantial evidence of the effectiveness of Lutrexin. In addition to this point, three basic jurisdictional questions were before the Court of Appeals and argued in HW&D's brief: (1) whether the Commissioner of Food and Drugs was correct in his determination that Lutrexin was not exempt from both *administrative* and *judicial* enforcement of the effectiveness provisions of the Drug Amendments of 1962, by virtue of Section 107(c)(4) of those amendments; (2) whether the Commissioner was correct in his determination that Lutrexin was not exempt by virtue of Section 107(c)(2) of the 1962 Amendments, from *administrative* withdrawal of approval of its NDA under Section 505(e)(3) of the Act on the ground of lack of substantial evidence of effectiveness, and (3) whether in any event the Commissioner was correct in determining that HW&D's product is a new drug subject to the provisions of Section 505 of the Act as amended by the 1962 Amendments. A hearing was denied on these questions.

The Court of Appeals decided the first jurisdictional question adversely to HW&D, following its decision in *USV Pharmaceutical Corporation* v. *Richardson* (4th Cir. No. 71-1596, May 24, 1972, App. C, 45a). It did not

even mention the second and third questions. On May 23, 1972, the day before its decision in the instant case, the Fourth Circuit had held that neither FDA nor the Court of Appeals on direct appeal under Section 505(h), 21 U.S.C. 355(h), had authority to determine the agency's jurisdiction. (*Bentex Pharmaceuticals, Inc.* v. *Richardson*, No. 71-1243, App. C, 29a). Implicit in the Court's decision in HW&D, because of its ruling in *Bentex*, is a holding that FDA did not have the authority to decide these jurisdictional questions.

It is apparent that factual questions underlie the matter of whether Sections 107(c)(2) and (4), or either of them, is applicable to Lutrexin, *viz.*, whether the drug was generally recognized as safe on the day before the effective date of the Drug Amendments of 1962 (October 9, 1962), within the meaning of Section 107(c)(2) and Clause (B) of Section 107(c)(4) of those amendments and was therefore not a new drug on that date; and whether the drug was being marketed in the United States on October 9, 1962 and the labeled conditions of use are now the same as on that date, within the meaning of Section 107(c)(4). Underlying the third jurisdictional question above stated is the factual matter of whether Lutrexin is generally recognized *now* as both safe *and* effective within the meaning of Section 201(p) as amended in 1962. These are adjudicative facts determinative of the jurisdictional questions involved (See affidavits of experts, Jt. App. I, 38 et seq.; medical literature, Jt. App. II).[6]

Because of the *Bentex* ruling, evidence on the factual questions above-stated would not be considered by FDA or introduced at the hearing to which the Court of Appeals said HW&D was entitled since the hearing would

[6] The reference to Jt. App. I and II is to the two volumes filed in the Court below and certified to this Court, and not to the Appendices to this petition.

be limited to the question of whether there is a lack of substantial evidence of the effectiveness of Lutrexin. Yet, if any one of the jurisdictional questions were decided in favor of HW&D, the question of whether HW&D is entitled to a hearing on the Commissioner's proposal to withdraw the license for its product under the new drug provisions of the Act would be moot.

REASONS FOR GRANTING THE WRIT

(1) Introduction

FDA's order withdrawing approval of the NDA for Lutrexin was based on the opinion of a panel of the National Academy of Sciences—National Research Council (NAS-NRC) that the drug was "possibly effective" for the conditions for which it is used.[7]

Lutrexin is one of more than three thousand drugs which were evaluated by panels of NAS-NRC.[8] FDA is still in the process of reviewing the reports of some panels. The status of an unknown but certainly a substantial number of these drugs which were evaluated as "possibly effective" or "probably effective", rather than "effective", will be determined by the interpretations given to the provisions of the Drug Amendments of 1962 here involved. For the reasons stated herein, we believe the Court of Appeals erred in its decision as to the application of Section 107(c)(4) of the 1962 amendments and in its failure to consider the effect of Section 107(c)(2).

---

[7] FDA had contracted with NAS-NRC to review the effectiveness of drugs cleared for marketing as "new drugs" between 1938 and 1962 on the basis of proof of safety only.

[8] The Court of Appeals for the District of Columbia recently characterized certain NAS-NRC reports as "cryptic and conclusory, without any statement of supporting facts". *USV Pharmaceutical Corporation* v. *Secretary of Health, Education & Welfare* (No. 24,900, August 14, 1972). The scanty report on Lutrexin may also be so described (See Jt. App. 5).

This case also concerns the fundamental question of whether an administrative agency has the authority to determine its own jurisdiction, subject to statutory review by the Court of Appeals, before acting upon matters before it. The Court of Appeals' decision on this point in *Bentex, supra*, which was followed in the instant case, is in direct conflict with the decision of the Court of Appeals for the Third Circuit in *Ciba Corporation* v. *Richardson*, 3rd Cir., Civil No. 71-1512, (June 5, 1972, App. D, 55a).

Moreover, we submit that in any event this cross-petition should be granted for the reason stated by this Court in granting the Government's petition in *United States* v. *An Article Of Drug, Etc.*, 394 U.S. 784, 791 (1969), *viz.*, that the interpretation involved raise issues of importance in the administration of the Federal Food, Drug and Cosmetic Act.

(2) The Authority Of FDA To Determine Initially Its Own Jurisdiction

The Court of Appeals ruled in *Bentex*, and followed that ruling in the instant case, that only a District Court in an enforcement action brought by the Government or in a declaratory judgment suit brought against the Government, has authority to determine whether and to what extent a drug is subject to the jurisdiction of FDA as a "new drug", that is, whether it is generally recognized as safe and effective and thus is not a new drug or whether it was exempt from the effectiveness provisions of the Drug Amendments of 1962 by Section 107 (c) (2) or 107 (c) (4) of those amendments. The District Court in *Bentex* had held that FDA had concurrent jurisdiction with that court to make such determinations, *O'Neal, Jones & Feldman, Inc.* v. *Richardson*, (D.S.C., Civil No. 70-1001, February 10, 1971). We agree with the District Court.

We have noted that the decision of the Court of Appeals that FDA has no authority to determine its own jurisdiction and that the Court of Appeals may not review such a determination, is in direct conflict with *Ciba Corporation* v. *Richardson*, (3rd Cir., Civil No. 71-1512, June 5, 1972). That Court said:

> "Inherent in the grant of administrative competency to conduct and decide new drug proceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such a proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision" (App. D, 55a, 56a).

The question here involved is of obvious concern to all persons who file NDAs or whose NDAs are the subject of withdrawal proceedings, as is the NDA for Lutrexin. It presents a basic issue of administrative competence to deal with matters whose resolution is essential to a proper disposition of new drug proceedings.

It would not make sense for FDA to withdraw approval of an application for Lutrexin, or any other drug, and for the Court of Appeals to review the order of withdrawal, without a decision upon the issue of whether the subject drug is "new" and therefore within FDA's jurisdiction. One subject to such a proceeding should not be *required* to commence another proceeding in the District Court to obtain initial adjudication of the agency's competence to conduct the administrative proceeding.

The Court of Appeals stated in *Bentex* that "The very filing of the [new drug] application is a concession and recognition by the applicant-manufacturer that the article is a 'new drug'; otherwise there would be no reason to file the application" (App. C(1), 29a, 42a).

This statement reveals a lack of understanding of the realities of the regulatory and public relations problems

of the drug industry. If FDA expresses the opinion that a drug is "new", manufacturers have frequently filed NDAs to avoid enforcement proceedings by FDA, despite their belief that the drug is in fact not a new drug. Litigation with FDA is not welcomed by industry and may cause unfavorable public reaction. The filing of an application may or may not, therefore, indicate a belief that the article is "new".

None of the cases cited by the Court of Appeals in *Bentex* was concerned with the issue of whether an agency has, initially, the authority to determine its own jurisdiction. Moreover, the fact that the jurisdictional question may be decided in enforcement and declaratory judgment actions does not preclude its determination by FDA in administrative proceedings. Evidence upon the question of general recognition can be taken at an administrative hearing as well as in a district court.

FDA and other agencies must constantly decide, initially, whether a particular product or subject matter is within their jurisdiction. It seems apparent to us that otherwise they could not function. The agency itself is in no position to ask a court to decide whether a drug is "new" when a new drug application is filed with it. It must decide the question itself, and has always done so, although it has not designated it as an issue at a hearing. If, on the other hand, the manufacturer of the drug is threatened with adverse action by FDA he should, we think it clear, be able to obtain a decision on the jurisdictional question in the District Court or, on appeal from an Agency determination, in the Court of Appeals.

We can see no reason to doubt that an agency must, where its jurisdiction is at issue, determine that issue before proceeding to decide the merits of other questions before it. It is so held by the courts, *Endicott Johnson Corporation* v. *Perkins*, 317 U.S. 501 (1943) (coverage of Walsh-Healy Public Contracts Act); *Oklahoma Press*

Pub. Co. v. *Walling*, 327 U.S. 186 (1946) (coverage of Fair Labor Standards Act).

We find nothing in the cases which supports the argument that FDA does not have the *authority* to determine, initially, its own jurisdiction. The fact that FDA had refused to make a formal determination on the question prior to the decision in *Hynson, Westcott & Dunning, Incorporated* v. *Finch* (D. Md., Civil No. 21112, decided September 16, 1970)[9] does not militate against this conclusion. It merely indicates that, prior to its change of policy on the matter, there was no adequate administrative remedy on the jurisdictional issue.

Orders of the National Labor Relations Board may be challenged, on jurisdictional grounds, either collaterally (*Leedom* v. *Kyne*, 358 U.S. 184, 188 (1958)), or in the Court of Appeals in an enforcement proceeding (*National Labor Relations Board* v. *Pappas & Co.*, 203 F.2d 569, 571 (9th Cir. 1953)). This, we submit, is the situation under § 505(h) of the Federal Food, Drug and Cosmetic Act. It seems clear to us that the Court of Appeals should, in reviewing an order withdrawing approval of a "new drug" application under that section, determine whether the article is a "new drug," if there is any doubt of its status. Such an order would be of no force or effect if the article were not a "new drug." The threshhold question in this case must be whether FDA correctly concluded that it had jurisdiction over Lutrexin as a "new drug." The question of the validity of the withdrawal of NDA approval for lack of substantial evidence of effectiveness would be moot if the threshhold question were decided in favor of petitioner.

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[9] This was a declaratory judgment suit seeking a declaration that Lutrexin was not subject to the jurisdiction of FDA under the withdrawal of approval provision of Section 505(e)(3). It was dismissed on the ground that FDA had primary jurisdiction. The dismissal was not appealed.

(3) Right To A Hearing On The Jurisdictional Questions

Section 505(e) and the decision of the Fourth Circuit, require that HW&D be afforded a hearing on the question of whether there is a lack of substantial evidence of effectiveness of Lutrexin before withdrawal of approval of the NDA.

It is our position, and the Court in *Ciba Corporation* v. *Richardson*, supra, held, that the authority to determine its own jurisdiction is inherent in the grant of authority to the agency to conduct new drug proceedings. The required hearing is such a proceeding and it appears to us that, where issues of jurisdiction have been raised, as here, the holder of the NDA is entitled to present evidence upon such issues. That is the only logical conclusion where the agency proposes to act under Section 505(e)(3).

Moreover, under the due process clause of the Constitution, we submit that the agency may not make adjudicative determinations (as distinguished from rule-making) without affording adversely affected parties a hearing.[10] The jurisdictional points raised by HW&D before FDA and the Court of Appeals involve substantial questions of adjudicative facts, *e.g.*, whether in any event Lutrexin is now generally recognized as safe and effective for its intended uses.

In the case at bar, FDA held Lutrexin to be a new drug and subject to the effectiveness provisions of the 1962 amendments, and rejected HW&D's request for a hearing on the underlying factual issues. HW&D had submitted to the agency affidavits and other data showing that it had a factual basis for its request for a hearing on these crucial issues. The denial of a hearing cannot, therefore, be justified on the ground that only legal ques-

[10] Davis, Administrative Law Treatise, 1970. Supplement, Sections 7.01, 7.04 and cases there cited.

tions were before the agency. The point was not even mentioned by the Court of Appeals, presumably because it was following its holding in the *Bentex* case that neither FDA in an NDA withdrawal proceeding pursuant to Section 505 of the Act, nor the reviewing court, has the authority to decide jurisdictional questions.

The Court of Appeals emphasized that under principles of due process and the requirements of the Administrative Procedure Act, HW&D was entitled to a hearing before approval of the NDA for Lutrexin could be withdrawn. Surely before, or at least in the course of, conducting a hearing pursuant to the new drug provisions of the Act, due process dictates a hearing on the question of whether Lutrexin is a new drug and subject to withdrawal of approval proceedings under Section 505(e)(3).

(4) Section 107(c)(4) Of The 1962 Amendments

Section 107(c)(4) of the 1962 Amendments specifically made the effectiveness requirements of the amendments inapplicable to drugs which on or before October 9, 1962, (A) were being marketed in the United States, (B) were not "new drugs" and (C) were not then "covered by an effective [new drug] application," if the labeled conditions of use were the same as on that date.

The Court of Appeals held that Lutrexin was not exempt under Section 107(c)(4) of the 1962 Amendments because approval of its NDA had not been withdrawn by FDA under Section 505(e). This construction distorts the purpose and effect of Section 505(e) and makes Section 107(c)(4) meaningless except as applied to so-called "me-too" drugs.[11]

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[11] These are copies of drugs which were once the subject of NDAs but then became "old drugs" thus opening the way for the copies to be marketed without NDAs. There are many such copies.

The *purpose* of Section 505(e) is to prevent the further shipment of a new drug in interstate commerce based upon a finding that it is unsafe or ineffective or otherwise fails to conform to the standards set up in Section 505(e). Obviously, this purpose is entirely inconsistent with the effect which the court attributes to such withdrawal, *viz.*, that it operates as a condition of the exemption of the drug under Section 107(c)(4).

Thus, the bizarre result of the court's ruling would be that such a drug (including Lutrexin) could become exempt by reason of withdrawal of approval under Section 505(e), whereas the intended effect under the statute is to prevent the shipment of the drug in interstate commerce on the basis of the FDA view that it is still a new drug which does not comply with Section 505.

We submit that a construction so clearly inconsistent with the purpose of the statute should not be allowed to stand.

Our position, and the evidence we have submitted, that Lutrexin was on the market on the day preceding the effective date of the 1962 Amendments (Clause (A) of Section 107(c)(4)) and that it was no longer a new drug on that date because it was then generally recognized as safe (Clause (B)) have not been challenged in this proceeding. In any event, the facts could be determined by FDA at a hearing. We maintain also that Lutrexin meets the test of Clause (C) because it was not covered by an "effective" NDA on that date.

We think it clear that an NDA for a drug which is no longer "new" within the meaning of the Act has no legal effect at all—is not viable in any way. Thus, if FDA purported to approve an application for a drug which was not "new" within the meaning of Section 201(p) the application would not be legally "effective" within the meaning of Clause (C) of Section 107(c)(4).

The Court of Appeals for the Fourth Circuit held in a related case [12] that this argument would make surplusage of Clause (C). It is true, as we have stated, that if a drug which had been NDA'd had ceased to be new on October 9, 1962, it would meet both tests (B) and (C) by reason of that fact.

By the same token, if, as FDA maintains, and the Court of Appeals agrees, every drug which had gone through the new drug procedures and had thereafter ceased to be a new drug was nevertheless "covered by an effective application" within the meaning of Clause (C), then Clause (B) would be surplusage; for if such a drug is "covered by an effective application" despite having lost its new drug status, the test of whether it is no longer a new drug (Clause B) would be useless.

Complementing the basic considerations above discussed is the circumstance that the language of §§ 107(c)(2), (3), and (4) of the Amendments leads clearly to the conclusion that only *new claims* of effectiveness for drugs whose NDAs became effective prior to October 10, 1962, were subject to the amendments. This view is supported by the legislative record of S. 1552, which, as revised, became the 1962 Amendments.

When the bill, as originally reported by the Senate Judiciary Committee, was changed to expand the definition of "new drug" to include drugs not generally recognized as effective, the Committee stated—

> "A question arose as to the circumstances and extent to which a new claim or change of claim of effectiveness made after the initial approval of a new drug application could be made without supporting evidence to be submitted to the Department under the new-drug procedure. In order to eliminate any

[12] *USV Pharmaceutical Corporation* v. *Richardson* (4th Cir., No. 71-1596, May 24, 1972, App. C(2) at 45a.

possible ambiguity on this point the term 'effectiveness' is employed in the committee's substitute amendment." [13]

Likewise, on the floor, Senator Eastland, consistently with the language of Sections 107(c)(2)(3), and (4), said that, with the addition of "effectiveness" to the definition "every brand new product, and every new claim for an existing product, would be subject to the tests and procedures established in § 505 of the Act".[14]

There is nothing inconsistent with these explanations in the history of HR 11581, the companion bill to S. 1552.

It must be clear from the legislative history as well as from the terminology of the 1962 Amendments themselves that (1) the fact that drugs which had never been subject to the new drug procedures were exempt from re-evaluation for effectiveness did not mean that other drugs, such as those which were no longer new drugs on October 9, 1962, were not also exempt and (2) that statements in the Committee Reports and in debate relating to withdrawal of approval of NDAs on the grounds of lack of effectiveness after two years from October 9, 1962, referred only to withdrawal of approval of NDAs for drugs which were still *new drugs* on that date.

(5) Section 107(c)(2) Of The 1962 Amendments

The Court of Appeals for the Fourth Circuit failed to mention a basic argument of HW&D that, under Section 107(c)(2) of the 1962 Amendments, an NDA which was 'effective' on the day immediately preceding the enactment date (i.e. October 9, 1962) is not "deemed approved" and consequently is not subject to withdrawal proceedings under Section 505(e)(3), 21 U.S.C. 355(e)

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[13] S. Rep. No. 1744, Part II, 87th Cong., 2d Sess. 5.

[14] 108 Cong. Rec. 16304 (August 23, 1962).

(3), which is applicable only to NDAs which have been actually approved (or "deemed approved") under the Act.

Under Section 107(c)(3)(B) of the 1962 Amendments, a drug whose application is "deemed approved" under Section 107(c)(2) is not subject to administrative withdrawal-of-approval proceedings under Section 505(e)(3) (lack of substantial evidence of effectiveness) for two years after the enactment date of the amendments.

FDA contended below that Lutrexin was "deemed approved" and approval of its NDA was, therefore, subject to withdrawal under Section 505(e)(3), two years after the enactment date. This theory was cited as legal justification for its withdrawal order (Jt. App. I, 95, 97).

Under the plain language of the statute, however, only those NDA's were "deemed approved" which were "effective" within the meaning of the basic Act on the day preceding the enactment date of the 1962 Amendments (October 9, 1962).

We have stated above our position that the NDA for Lutrexin was no longer "effective" on October 9, 1962, Lutrexin being no longer a new drug. The affidavits of experts which are part of the record state that the drug was generally recognized as safe on that date—the test of whether it was then a new drug. If it was no longer a new drug its NDA no longer had viability—was of no legal effect.

We submit that it is clear that the only drugs "deemed approved" were those which, on October 9, 1962, were still new drugs because they were not then generally recognized as safe.

It should be emphasized that our conclusion that Lutrexin was not "deemed approved" excuses it from administrative withdrawal of approval of its NDA under Section 505(e)(3), but not from judicial proceedings such

as seizure, criminal prosecution and actions for injunctions based on allegations of lack of effectiveness.[15] It is exempt from these judicial proceedings only if it meets the three conditions of Section 107(c)(4) above considered and then only with respect to old claims of effectiveness being made on October 9, 1962.

If scientific developments should result in a re-evaluation by qualified experts and a reversal of their recognition of safety, FDA could proceed in the District Court against the drug on the ground that it had again become a new drug under Section 201(p). Moreover, as we have stated, if the agency believes that the claims of effectiveness for an exempt drug are false or misleading it can proceed against them under Section 502(a) of the Act. There is no exemption from such a proceeding.

FDA is therefore not without effective remedies. The fact that it cannot challenge the status of drugs such as Lutrexin under Section 505(e)(3) with respect to old claims of effectiveness results from a deliberate choice of the Congress.

We submit that these questions of the correct interpretation of basic provisions of the Drug Amendments of 1962, involving as they do the status of hundreds of drugs, should be resolved by this Court. The Court of Appeals, we believe, was clearly wrong in its interpretation of Section 107(c)(4) and in its failure to consider petitioner's argument that Lutrexin (and many other drugs) were not "deemed approved" under Section 107(c)(2). Petitioners and the many other manufacturers of drugs in a position similar to that of HW&D should

[15] Section 505(a), 21 U.S.C. 355(a): "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug." Section 301, 21 U.S.C. 331: "The following Acts and the causing thereof are hereby prohibited: . . . (d) The introduction or delivery for introduction into interstate commerce of any article in violation of section . . . 505."

not have to accept the determination of the Court of Appeals as final. If, in the future, another Court of Appeals should rule differently, many drugs will have been forced from the market so that a decision by this Court would come too late.

Moreover, a serious and basic question of administrative law extending beyond the Federal Food, Drug and Cosmetic Act, is presented here—the authority of an administrative agency to determine its own jurisdiction in proceedings dealing with matters brought before it.

Finally, it is submitted that HW&D, as a participant in new drug proceedings before FDA is entitled, as a part of such proceedings, to a hearing on the facts underlying the jurisdictional questions involved, where, as here, jurisdictional issues have been raised.

CONCLUSION

For the foregoing reasons the cross-petition for a writ of certiorari should be granted.

Respectfully submitted,

EDWARD BROWN WILLIAMS
Counsel for Cross-Petitioner

September, 1972

APPENDIX A

Statutes Involved

Federal Food, Drug and Cosmetic Act

(52 Stat. 1040, as amended, 21 U.S.C. 301 et seq.)

Section 201(p), 21 U.S.C. 321(p), as amended by the Drug Amendments of 1962, P.L. 87-781:

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

Section 502, 21 U.S.C. 352:

A drug or device shall be deemed to be misbranded—

(a) If its labeling is false or misleading in any particular.

Section 505, as amended, 21 U.S.C. 355:

SEC. 505 [355]. (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of

substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to

him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j), or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any

particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

(f) Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28, United States Code. Upon the filing of such petition such court shall have ex-

clusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

The Drug Amendments of 1962, P.L. 87-781, provide in part:

EFFECTIVE DATES AND APPLICATION OF PART A

SEC. 107. (a) Except as otherwise provided in this section, the amendments made by the foregoing sections of this part A shall take effect on the date of enactment of this Act.

(b) The amendments made by sections 101, 103, 105, and 106 of this part A shall, with respect to any drug, take effect on the first day of the seventh calendar month following the month in which this Act is enacted.

(c) (1) As used in this subsection, the term "enactment date" means the date of enactment of this Act; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.

(2) An application filed pursuant to section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date by virtue of paragraph (2) of this subsection—

(A) the amendment made by this Act to section 201(p), and to subsections (b) and (d) of section 505, of the basic Act, insofar as such amendments relate to the effectiveness of drugs, shall not, so long as approval of such application is not withdrawn or suspended pursuant to section 505(e) of that Act, apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested

in labeling covered by such approved application, but shall apply to any changed use, or conditions of use prescribed, recommended, or suggested in its labeling, including such conditions of use as are the subject of an amendment or supplement to such application pending on, or filed after, the enactment date; and

(B) clause (3) of the first sentence of section 505 (e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application (except with respect to such use, or conditions of use, as are the subject of an amendment or supplement to such approved application, which amendment or supplement has been approved after the enactment date under section 505 of the basic Act as amended by this Act) until whichever of the following first occurs: (1) the expiration of the two-year period beginning with the enactment date; (ii) the effective date of an order under section 505(e) of the basic Act, other than clause (3) of the first sentence of such section 505(e), withdrawing or suspending the approval of such application.

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

APPENDIX B

Order and Opinions Below

(1) The Order of the Commissioner of Food and Drugs withdrawing approval of the new drug application for Lutrexin (36 F.R. 11763).

HYNSON, WESTCOTT & DUNNING, INC.

Notice of Withdrawal of Approval of New-Drug Applications

On March 22, 1969, there was published in the FEDERAL REGISTER (34 F.R. 5556) a notice of opportunity for hearing in which the Commissioner of Food and Drugs proposed to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) withdrawing approval of new-drug applications for drugs containing lututrin on the ground that there is a lack of substantial evidence that lututrin has the effect or contributes to the effect which the drugs purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.

Hynson, Westcott & Dunning, Inc., Charles and Chase Streets, Baltimore, Md. 21201, holder of NDA No. 8-986, Lutrexin tablets and NDA No. 10-144, Trexinest tablets by the October 16, 1970 letter of its counsel, has requested a hearing on the following issues:

(1) Whether its lututrin drugs are exempt from the efficacy requirements of 21 U.S.C. 355 under section 107 (c) of Public Law 87-781; (2) whether its lututrin drugs are "new drugs" within the meaning of 21 U.S.C. 321(p)(1); and (3) whether there is a lack of substantial evidence of effectiveness to support the claims made for Lutrexin.

In support of its request for a hearing on the issue of substantial evidence of effectiveness, Hynson, Westcott, and Dunning, Inc. (hereinafter referred to as "HW&D") has submitted a list of its medical documentation previously filed with the Agency, including all data submitted in connection with NDA No. 10-144, correspondence between HW&D officials and the Agency or other persons, labeling for the lututrin drugs, literature articles submitted to the National Academy of Science-National Research Council, and the HW&D letter of August 18, 1969, in which the company first elected to avail itself of the opportunity for hearing.

To support its hearing request on the contentions that HW&D's lututrin drugs are exempt from the efficacy requirements of 21 U.S.C. 355, the company has submitted copies of its pleadings, legal memorandum, exhibits, and affidavits, as well as the transcript and order in Hynson, Westcott and Dunning, Inc. v. Finch (C.A. No. 21112, D. Md., decided Sept. 11, 1970).

The Commissioner of Food and Drugs has reviewed HW&D's request for hearing and the medical documentation submitted, and makes the following findings:

I. *The drugs, their rationale and claims.* a. Lutrexin is labeled as containing 3,000 units of lututrin per tablet. Lututrin is claimed to be a pig uterine relaxing hormone effective in the treatment of functional dysmenorrhea, selected cases of premature labor and threatened and habitual abortion. The package insert claims the drug has demonstrated activity on the living animal uterus, that it relaxes the contracted uterine muscle by direct action thereon, or by blocking pituitary action.

b. Trexinest is labeled as containing 500 units of lututrin and 1.0 milligrams of estrogen, in the form of sodium estrone sulfate, per tablet. Trexinest is recommended for the treatment of menopausal disorders. The

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package insert claims that the combination is more effective than lututrin or estrogen alone and points to lututrin as the responsible agent in the drug's effectiveness.

II. *The applicable regulations.* HW&D's contention that it has an unconditional right to a hearing is denied. The hearing regulations, 21 CFR 130.14, require that a person seeking a hearing set forth specific facts showing the existence of genuine and substantial fact issues which requires a hearing. The order of May 8, 1970 (35 F.R. 7250) granted persons involved in notices of hearing, including HW&D, 30 days in which to amend their requests for hearing to comply with the new regulations. The company was given actual notice on May 19, 1970, that it was required to comply with these regulations in order to properly avail itself of an opportunity for hearing. Applications of the regulations have been upheld by the courts. Pfizer, Inc. v. Richardson, 434 F. 2d 536 (C.A. 2, 1970); Upjohn Co. v. Finch, 422 F. 2d 944 (C.A. 6, 1970); Pharmaceutical Manufacturers Association v. Richardson, 318 F. Supp. 301 (D. Del., 1970). HW&D is bound by the judgment in the last case cited.

III. *The Request for a Hearing*—a. *The issues of exemption under section 107(c) of Public Law 87-781 and under 12 U.S.C. 321(p)(1).* The request for a hearing on these issues is denied. The new-drug applications involved had not been withdrawn prior to enactment of Public Law 87-781. They were "deemed approved" under the 1962 amendments to the Act and are subject to withdrawal on the basis of the effectiveness requirements of the amendments.

b. *Lutrexin and Trexinest are new drugs within the meaning of 21 U.S.C. 321(p)(1).* The conclusions of HW&D's affiants that these drugs are not new drugs cannot be accepted. No adequate and well-controlled clinical investigations published in the medical literature

have been identified. Therefore, there is no data base upon which experts can fairly and responsibly conclude that the safety and effectiveness of the drugs has been proven and is so well established that the drugs can be generally recognized among such experts as safe and effective for their intended uses.

The affiants identify 11 studies as establishing the claims made for the drugs. None purports to be an adequate and well-controlled clinical investigation. They may be summarized as follows:

(1) Majewski and Jennings: Uterine Relaxing Factor for Premature Labor, Ob. & Gyn. 5:649-652 (May 1955); and Further Experiences with a Uterine Relaxing Harmone in Premature Labor, Ob. & Gyn. 9:322-325 (March 1957) by the same authors are one study. The first paper is a preliminary study on 20 patients and the latter is the report on enlarged group of 88 patients. The authors acknowledge that results in the total group are less favorable than in the preliminary study, but conclude that the results are encouraging. Concomitant medication was given an unstated number of patients. There is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced. Nine patients out of 88 in whom the drug proved ineffective were excluded from the report for "statistical reasons". Six patients received the drug for less than 3 hours, which the authors without explanation considered too short a time for a true test of effectiveness. There is no summary or explanation of the statistical methods used in analysis of the data to show that results were not biased or due to chance.

(2) Majewski: Statistical Evaluation in The Reduction of the Incidence of Prematurity (1968) is unpublished. The author claims successful treatment in 86 percent of cases treated in his practice over a 10-year period. Substantiating documentation to establish an

historical control and percentage of patients with medical or surgical complications of pregnancy is not provided. The author acknowledges that some patients with medical complications such as placenta praevia were included in the study. Lutrexin is not claimed to have value in the medical or obstetrical complications of pregnancy which occur in a significant percentage of premature births.

The pairing of live birth percentages by number of pregnancies before and after Lutrexin treatment such as in Table I are all inappropriate. For example, of the 24 cases with one previous pregnancy, 11 live births before treatment and 18 live births after treatment are compared. However, for each of the 18 live births after treatment, an additional pregnancy had elapsed so that the number of previous pregnancies associated with the number 18 is two, not one; as such, the number 18 should be compared with the number 16, the total live births for two previous pregnancies.

The data in Table I does not admit of statistical evaluation by the chi-square test since the test is based on the assumption that each number in the columns of Table I is the sum of independent yes or no responses, e.g., for the one patient with seven previous pregnancies, four live births are correlated, thus ignoring the sample size of one and using an erroneous sample size of four.

(3) Rezek: The Effect of a New Potent Uterine Relaxing Factor of the Corpus Luterum in the Treatment of Dysmenorrhea, Am. J. Ob. & Gyn. 66:396-402 (August 1953). The report does not state the method of patient selection, nor does it indicate comparability of pertinent variables such as severity or duration of diseases. Concomitant medication is not excluded. No explanations of the methods of observation, the recording of results, and steps taken to minimize patient and in-

vestigator bias are provided. The historical controls employed are inappropriate.

(4) Rezek: Lutrexin in the Treatment of Premature Labor, Ann. N.Y. Acad. Sci. 75:995-997 (January 1959). The method of selection of the patients does not show progressive dilation of the cervix, which is necessary to accurately diagnose premature labor. The methods of observation and the recording of results are not explained. No statistical evaluation was presented to show that results claimed are significant in terms of the patient population.

(5) Gratton: The Treatment of Infertility and Prematurity Pregnancy Problems (1968) is unpublished. Patients received numerous concomitant therapies until the fifth month of pregnancy which prevents scientific attribution of results to lututrin therapy. The method of patient selection is unexplained.

Statistically the study lacks adequate design and evaluation. There is no showing that the cases studied are representative of the population to which inferences are made. The pairings of live births percentages in Table II cannot be compared since the number of previous pregnancies differs between the pair percentages and there is no data on possible etiologic factors of previous abortions and premature labor.

(6) Gray: Lutrexin in the Management of Premature Labor and Habitual Abortion. A Description of Fifteen Representative Cases (undated) is an unpublished report on 15 selected cases the author has treated. No plan or protocol is provided to allow determination of the objectives of the study, the method of patient selection, diagnostic criteria of the condition to be treated, laboratory tests to be made, the methods of observation and recording of results. The author's review of his records does not constitute an adequate and well-controlled investigation.

(7) Four papers by Dr. Trythall were listed in the attachment to his affidavit. In only one article is lutrexin ever mentioned.[*] The three sentences devoted to the drug provide no information whatsoever except that the author claims to have found it effective in his practice.

The affiants state that double blind investigations of lututrin are unethical because the drug is effective and complications of pregnancy may be life-threatening. The Commissioner does not reach that issue, since none of the historically controlled studies relied upon were adequate and well-controlled investigations.

There are other reasons why HW&D's medical data lack merit, but in view of the above finding their delineation is unnecessary.

c. *The issue of substantial evidence of effectiveness.* The request for a hearing on this ground is denied. The regulations, 21 CFR 130.14, require HW&D to submit a well organized and full factual analysis of the clincial and other investigational data it is prepared to prove at a hearing. The request must set forth specific facts showing that there is a genuine and substantial issue of fact requiring a hearing. HW&D has not attempted compliance with these requirements.

Rather than identify and discuss the efficacy data relied upon to support the claims made for its drugs, the company has merely provided a list, extending to four pages, of practically all materials ever submitted to the Agency and the NAS-NRC. The materials are described, for the most part, in general terms (e.g., "data submitted in connection with New Drug Application for Lutrexin tablets * * *, Lutrexin bibliography * * *, Trexinest bibliography * * *, reprints and abstracts * * *). What the Commissioner is required to do is

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[* Lutrexin is in fact discussed in two of the papers (Jt. App. II, 64 and 68)].

determine from this material, what HW&D may or may not consider relevant and, therefore, relies upon. In the case bibliographies, the Commissioner would be required to research each article and then determine if it is relevant, or whether HW&D might consider it relevant. Because such a procedure is not contemplated by the regulation, the request for hearing is denied for failure to comply with applicable regulations.

Apart from the refusal of HW&D to comply with 21 CFR 130.14, the most basic material in the Lutrexin new-drug application reveals a lack of adequate and well-controlled investigations showing that lututrin will have the effect HW&D claims for it.

The only evidence submitted that lututrin may have biological activity in humans when taken orally is a test on nine women by Jones and Smith in which positive results were reported to have been obtained in six subjects. No plan or protocol was stated. No data on the participating patients was provided. No explanation of procedures for patient selection, or criteria for inclusion in the study, or appropriate laboratory tests before and after administration of lututrin was provided. No statistical analysis showing the test population was of significant size or that results obtained were significant is shown. Moreover, there is no evidence that results claimed have ever been reproduced in humans by other investigators.

Therefore, the Commissioner of Food and Drugs, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 505(e), 52 Stat. 1053, as amended; 21 U.S.C. 355(e)), and under the authority delegated to him (21 CFR 2.120), finds that on the basis of new information before him with respect to each of said drugs, evaluated together with the evidence available to him when each application was approved, there is a lack of substantial evidence that each of the drugs will have the

effects it is purported or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof.

Pursuant to the foregoing findings, approvals of the above new-drug applications, and all amendments and supplements thereto, are withdrawn effective on the date of the signature of this document.

Dated: May 31, 1971.

CHARLES C. EDWARDS
Commissioner of Food and Drugs

[FR Doc. 71-8557 Filed 6-17-71; 8:46 am]

APPENDIX B

(2) Opinion of the United States Court of Appeals for the Fourth Circuit, CCH Food, Drug, Cosmetic Law Reporter, ¶ 40,666.

UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 71-1717

HYNSON, WESTCOTT AND DUNNING, INCORPORATED,
Petitioner,

—versus—

ELLIOT RICHARDSON, Secretary of Health, Education and Welfare and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Respondents.

On Petition to Review an Order of the Commissioner of Food and Drugs

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(Argued February 7, 1972. Decided May 24, 1972.)

Before BUTZNER, RUSSELL and FIELD, Circuit Judges

RUSSELL, CIRCUIT JUDGE:

The appellant, a drug manufacturer, seeks review of a final order withdrawing marketing approval (NDA) of the drug Lutrexin by the Commissioner of Food and Drugs, Department of Health, Education and Welfare.[1] The appellant alleges error in such order of withdrawal (1) for failure to sustain its claim of exemption from

[1] Section 355(h), 21 U.S.C.

withdrawal on account of lack of "substantial evidence" of effectiveness of its drug and, if this claim of exemption is overruled, (2) for denial of a hearing, as required under the applicable statute, on its showing of effectiveness. We reverse.

The appellant was granted an approved NDA for Lutrexin in 1952 [*sic*]. At that time, the Food, Drug and Cosmetic Act of 1938 conditioned such grant on general recognition of safety of the drug approved. In 1962 the Act was amended to authorize withdrawal of an approved NDA for any drug for which the Commissioner "after due notice and opportunity for hearing", found there was "a lack of substantial evidence of effectiveness.[2] The term "substantial evidence" was defined in the Amendments as "consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."[3] There was an exemption from these requirements for drugs, which, *inter alia*, were not covered on the day immediately before the enacting date of the Amendments (i.e., October 9, 1962) by an "effective NDA".[4]

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[2] Section 355(e), 21 U.S.C.

[3] Section 355(d), 21 U.S.C.

[4] In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force * * *, and (C) was not covered by an effective application under section 505 of that Act * * *, the amendments to section 201(p) * * * made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day." Section 107(c)(4), appended to Section 321, 21 U.S.C., 1972 Supplement, p. 192.

In carrying out his new responsibilities under the Amendments, the Commissioner secured the services of the National Academy of Sciences-National Research Council (NAS-NRC) for reviewing the claims of effectiveness on behalf of any drugs NDA'd between 1938 and 1962.[5] To facilitate its assignment, NAS-NRC set up a Drug Efficacy Study Group and all drug manufacturers with approved NDAs obtained between 1938 and 1962 were directed by the Commisioner to submit to this Group evidence "pertinent to the evaluation of the effectiveness of the(ir) drugs."[6] The appellant submitted to the Group clinical data, investigations and studies in support of the effectiveness for its drug Lutrexin. After considering such data, NAS-NRC concluded that Lutrexin was "possibly effective" but indicated the supporting documentation was inadequate. The Commissioner advised the appellant of his concurrence with the conclusions of NAS-NRC and, as required by the statute, extended to it an opportunity for a hearing on the proposed withdrawal of the approved NDA for Lutrexin.[7] At such a hearing, the appellant was advised it might "produce evidence and arguments why approval * * * should not be withdrawn."[8] The appellant in due time requested such hearing. Under the Commissioner's regulations, a hearing was required within 90 days after such request, unless the parties agreed otherwise.[9] However, although no delay was agreed on, hearing within such period was not had. The delay on the part of the Commissioner in setting a hearing was due to litigation over the procedure to be followed by it in implementing its efficacy review and in conducting hearings resulting

[5] 21 F.R. 13014, October 6, 1966.

[6] 21 F.R. 13014.

[7] 33 F.R. 7701.

[8] 34 F.R. 5556.

[9] 21 C.F.R. 130.14(b).

therefrom.[10] It is unnecessary to review the difficulties encountered in developing valid regulations for such hearings. It is sufficient for the issues here that it was not until May 8, 1970, that the legal objections to the regulations were finally resolved. During this interregnum when the regulations of the Agency were under challenge and the Commissioner was delaying a hearing, the appellant, whose request for a hearing had been delayed for more than a year, sought in District Court a declaratory judgment to the effect that, under the exemption clause included in the 1962 Amendments, Lutrexin was not a "new drug" on and before October 10, 1962, and was thereby exempt from the requirement of evidence of effectiveness under the Amendments. Such action was dismissed on the ground that primary jurisdiction to resolve the issue of exemption under the Act rested with the Commisioner. No appeal was taken from this dismissal.

While this declaratory action was pending, the Commissioner issued his new regulations detailing the circumstances under which an applicant might secure a hearing on a proposal by the Commissioner for withdrawal of an effective NDA. By these regulations, the Commissioner was authorized to deny a hearing, "When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such

[10] See *Pharmaceutical Manufacturers Association* v. *Finch* (D.C. Del. 1970) 307 F. Supp. 858; *Upjohn* v. *Finch* (6th Cir. 1970) 422 F.2d 944; and *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F.2d 586.

data".[11] After the regulation had been legally promulgated, which was more than a year after the appellant had requested a hearing, the Commissioner directed the appellant's attention to these new regulations and suggested that it amend its request for a hearing to comply. Though it contended it had, by its earlier request, perfected its right to a hearing and was not obligated to amend its request, the appellant did, following the dismissal of its declaratory action, submit a considerable amount of clinical medical studies and investigations in support of the claim of effectiveness for its product by way of compliance with the new regulations. The Commissioner, however, dismissed the appellant's request for a hearing on the basis of such showing, finding (1) that its drug was a "new drug" requiring proof of effectiveness, and (2) that its showing of effectiveness was insufficient to demonstrate a "genuine and material issue of fact" under the test of "substantial evidence" as defined in the Amendments. On the basis of these findings it withdrew the approved NDA for Lutrexin. It is from this order that appeal has been taken.

I

The appellant's claim to an exemption for its drug is easily disposed of. We have held in a related case that a drug covered by a pre-1962 approved NDA, which had not been withdrawn under the procedure set forth in Section 505(e), is not entitled to the exemption granted under Section 107(c)(4) of the Amendments.[12] The appellant's NDA was outstanding and had not been legally withdrawn on October 10, 1962. It cannot accordingly claim the benefit of the exemption statute for its drug. While the appellant was entitled to have this issue resolved by the District Court, it was not prejudiced by, and cannot complain of, the refusal by the District Court

[11] 21 C.F.R. 130.14(b).

[12] *USV Pharmaceutical Corp.* v. *Richardson*, (4th Cir. 1972) —— F.2d ——.

to exercise jurisdiction. Nor, for that matter, did the appellant appeal and is accordingly without standing in this proceeding to challenge that dismissal.

II

The crucial issue in this case, however, is posed by the appellant's second contention and revolves about the requirement in the Act that, before the entry of a final order of withdrawal, the applicant be given an "opportunity for hearing". At such a hearing, the procedure adopted by the Commissioner allows the applicant to "produce evidence and arguments to show why approvals of (its drugs) * * * should not be withdrawn." [12a] Of course, the Commissioner might, as he did by his regulations issued in 1970, provide for the denial of a hearing where it clearly appeared from the applicant's own showing there was no "genuine and substantial issue of fact" on which the claim of the applicant might be sustained. *Ciba-Geigy Corp.* v. *Richardson* (2d Cir. 1971) 446 F. 2d 466, 468. It may be assumed that such regulation, when issued will apply to all pending applications. *U. S.* v. *Storer Broadcasting Co.* (1956) 351 U.S. 192, 205. But, in applying this regulation and in making his determination thereunder, the Commissioner's discretion is not absolute. Neither due process nor the Administrative Practice [*sic*] Act permits an arbitrary denial in any case where it can be fairly said there are "genuine and substantial issues of fact" in dispute.[13] Such

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[12a] Whether this is too narrow and improperly confines the scope of the hearing, so far as it is adjudicatory, see Davis, *The Requirement of a Trial-Type Hearing*, 70 Har. L.Rev. 193 (1956).

[13] See *Ciba-Geigy Corp.* v. *Richardson, supra*, at p. 468. The question is analogous to that presented by a demand for a hearing in connection with an N.L.R.B. election where the right to a hearing subject to the same general limitations as stated in the Commissioner's regulations, and it would seem the same test of the right to a hearing is applicable. For the rule in such N.L.R.B. case, see *N.L.R.B.* v. *Bata Shoe Co.* (4th Cir. 1967) 373 F.2d 821, 825-6; *United States Rubber Co.* v. *N.L.R.B.* (5th Cir. 1967) 373 F.2d 602, 606; *N.L.R.B.* v. *Smith Industries, Inc.* (5th Cir. 1968) 403 F.2d 889, 892-5.

a denial would, in addition, be violative of the Congressional purpose expressed in the provision for a hearing. And the courts must see that such Congressional purpose is not thwarted by administrative usurpation; or, as the Court said in *Environmental Defense Fund, Inc.* v. *Ruckelshaus* (D.C.C.A. 1971) 439 F. 2d 584, 596, the courts have "an obligation to ensure that the administrative standards conform to the legislative purpose * * *." Accordingly, only if it can be fairly said that the clinical tests and medical studies and investigations submitted by the applicant, if credited and accepted, will not support a finding that they provide "substantial evidence" of effectiveness was it proper for the Commissioner to deny the appellant a hearing *before* entering a final order of withdrawal. The judicial test is somewhat the converse of that to be applied in a review of a decision of the Commissioner entered *after* a hearing. In that instance, his decision is to be upheld, if sustained by any substantial evidence.[14] But in determining whether the Commissioner acted within the limits of his discretion on the procedural question of whether a hearing is to be allowed, the test is whether there is any "genuine and substantial" evidence that supports the position of the applicant. Manifestly, the applicant does not have to satisfy or convince the Commissioner by his evidence that his product is effective as a predicate for securing his right to a hearing. If that was his burden, a hearing would never be necessary or appropriate. If he, by his showing, convinced or satisfied the Commissioner, the proposed withdrawal would naturally be denied; on the other hand, if he failed to satisfy, then the Commissioner would deny a hearing and order withdrawal. In either event, a hearing would be useless and the Congressional promise of a hearing would be purely illusory. No such exacting standard of proof is required as a basis simply

[14] Section 355(h), 21 U.S.C.

for the right to be heard; as has been observed, all that is required for securing a right to a hearing is that the showing be such that, if accepted, a finding of "substantial evidence" of effectiveness would be supportable. And "substantial" in this connection does not mean "preponderant evidence" or "conclusive evidence". Congress specifically discarded those terms for the milder term "substantial", which was understood to embrace the idea, not of a preponderance but rather of a responsible body of qualified opinion.[15]

Applying the foregoing principles, we are of opinion the showing of the appellant was such that, under a reasonable construction of the Commissioner's own regulations, as well as under familiar principles of due process, and the requirements of the Administrative Procedure Act, it was entitled to an impartial hearing before its NDA was withdrawn. It must be noted that no qualified expert has given an opinion that Lutrexin is in-

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[15] In the course of committee deliberation a distinction evolved . . . between two tests—the "preponderant evidence" test and the "substantial evidence" test as now specifically defined. Under the former a claim would not be accepted under the new drug section unless it represented the preponderant view of experts . . . the committee recognizes that in the difficult area of drug testing and evaluation there will frequently, if not usually, be a difference of responsible opinion. The committee feels the existence of such a difference should not result in disapproval of a claim of effectiveness if it is supported by substantial evidence defined in the manner set forth below [that is adequate and well controlled investigations by qualified experts upon the basis of which conclusions made [*sic*] be fairly and responsibly drawn.].

[Application of the substantial evidence test means that] a claim could be rejected if it were found (a) that the investigations were not "adequate"; (b) that they were not "well-controlled"; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which its application is made; or (d) that the conclusions to be drawn by such experts could not fairly and responsibly be derived from their investigation.

S. Rep. No. 1744, 87th Cong., 2nd Sess. Part II, pp. 5-6, and see, 2 U.S. Code Congress. & Administrative News, 87th Cong., 2d Sess., p. 2892 (1962).

effective for the uses intended. The NAS-NRC review concluded it was "possibly effective". Neither is there any contention that it is unsafe when used for the purposes intended. The real basis for the determination by the Commissioner that the appellant had failed to make a showing of any genuine issue of fact on the effectiveness of its drug was the conclusion that the various scientific articles and tests submitted by the appellant were not "adequate and well-controlled clinical investigations" within the statutory definition of "substantial evidence". In his decision, the Commissioner sought to point out the deficiencies in the investigations submitted by the appellant which justified this conclusion. In so doing, he did not impugn the competency or qualifications of the scientists and medical experts whose investigations were cited by the appellant in support of its claim. Their professional qualifications, as they appear in the record, are impressive. Their investigations and opinions, some of which have been published in recognized professional medical journals, are, however, dismissed by the Commissioner with the statement that, "No adequate and well-controlled clinical investigations published in the medical literature had been identified". In making that statement, he disregards the categorical opinion of his former Director of the Bureau of Medicine and Medical Director that the clinical tests and investigations submitted by the appellant represented " 'well-controlled' clinical studies". He proceeds to fault two investigations published in an authoritative medical journal, submitted by the appellant, because, "There is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced", and "There is no summary or explanation of the statistical methods used in analysis of the data to show that results were not biased or due to chance". Another unpublished investigation is dismissed because, "Substantiating documentation to estab-

lish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided". Two published studies by a clinical professor of Obstetrics at the University of Illinois are criticized, in one instance, because "The report does not state the method of patient selection" and "Concomitant medication is not excluded" and, in the other, because "The method of selection of the patients does not show progressive dilation of the cervix, which is necessary to accurately diagnose premature labor." Assuming that all the objections by the Commissioner to these clinical studies, conducted as they were by competent medical authorities, may have some validity, they do not justify a final conclusion, made *ex parte*, without a hearing, that it "clearly appears" that there is no genuine issue of fact on the effectiveness of Lutrexin, which is the test under the Commissioner's own regulation for denial of a hearing; at most, they merely create a genuine question of fact to be resolved at a hearing upon proper evidence. Whether the studies were as controlled as they might have been and whether there was a failure in these studies as published to fill in all the details the Commissioner might think appropriate are matters that could be developed at a hearing, after the authors were examined and the reliability of the investigations further inquired into.

The order of the Commissioner, from which this appeal is taken, is set aside for failure to provide the petitioner with an "opportunity for a hearing" before the entry of said order.

REVERSED.

APPENDIX C(1)

Opinions In Related Cases

UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 71-1243

BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMACEUTIAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC., SOUTHERN DRUG & MFG. CO., THE BLAINE COMPANY, BROWN PHARMACEUTICAL CO., MAYRAND, INC., PHARMACEUTICAL ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHARMACEUTICALS, INC., BCR PHARMACAL CO., INC., ALTO PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES, INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMACEUTICALS PRODUCTS, INC., FOS PHARMACEUTICAL CO., W. E. BOODY & CO.,

Appellants,

—versus—

ELLIOT P. RICHARDSON, SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION,

Appellees.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF SOUTH CAROLINA, AT GREENVILLE. ROBERT W. HEMPHILL, DISTRICT JUDGE.

(Argued December 8, 1971 Decided May 23, 1972)

Before WINTER, RUSSELL and FIELD, Circuit Judges

RUSSELL, CIRCUIT JUDGE:

This appeal turns on a construction of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1962.[1] 21 U.S.C. 301, *et seq.* This statute requires pre-marketing approval and clearance of any "new drug" by the Secretary of Health, Education and Welfare.[2] The term "new drug" is defined as one "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof * * *."[3] From a denial of a pre-marketing approval or a withdrawal of a previously given approval, an appeal, originally to the District Court, now

[1] There was an earlier Food and Drug Act of 1906. 34 Stat. 768 (1906). It did not provide for any pre-marketing review of the safety of drugs. The sulfanilamide episode in 1938 prompted the enactment of the Federal Food, Drug and Cosmetic Act of that year to replace the earlier Act and to provide, *inter alia*, for such pre-marketing review of "new drugs". See C. W. Dunn, *Federal Food, Drug and Cosmetic Act—A Statement of Its Legislative Record*, pp. 1316-27 (1938). The fears generated by the thalidomide tragedies gave the impetus for the Amendments of 1962. See Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, 185 at p. 191, n. 45 (1971).

[2] Section 355(a), 21 U.S.C.

The actual approval of a "new drug" under the Act is normally processed by the Food and Drug Administration (FDA) in the Department of Health, Education and Welfare (HEW), and the approvals, when granted, are generally referred to as New Drug Approvals (NDAs). FDA, when used herein, refers to the Food and Drug Administration, and NDA is intended to describe an approval by FDA of a "new drug" application under the Act.

[3] Section 321 (p) (1), 21 U.S.C.

See, also, *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F. Supp. 443, 445, n. 2:

> "The statutory definition of the phrase 'new drug' controls this case, regardless of any other meaning attributable to the phrase or to the word 'new' by common understanding or other authority."

to the Circuit Court of Appeals, is authorized.[4] Drugs, which do not fit the definition of a "new drug" do not require FDA clearance for marketing. There is no provision in the Act for administrative determination whether a particular drug is a "new drug" nor for any right of appeal from any such determination. The FDA sometimes offers to render "informal advice" as to whether it considers a product a "new drug" but it uniformly designates such opinion "advice." [5] Accordingly, the responsibility for determining whether its product is a "new drug," requiring pre-marketing clearance by FDA, rests on the manufacturer, who must act at its peril.[6] If it makes an incorrect determination and seeks to market without FDA clearance a drug meeting the definition of a "new drug," it lays itself open to drastic judicial procedures that may be invoked by FDA, i.e.: The product may be seized in an *in rem* action instituted by the Government; [7] its sale may be enjoined in an action begun by the Government; [8] in addition, the manufacturer may be subjected to criminal action.[9] All these remedies must be prosecuted in the District Court and the role of the Secretary is that of plaintiff or prosecutor. The Act thus establishes two forum for the regulation of drugs: One is administrative and deals with the procedures for securing pre-marketing clearances for the statutorily defined "new drug," with right of appeal from a denial of

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[4] Section 355(h), 21 U.S.C.

[5] 21 C.F.R. 130.39.

[6] Cf. *United States* v. *Dotterweich* (1943) 320 U.S. 277, 281, where, speaking of the Act of 1938, the Court said:

> "In the interest of the larger good it puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger."

[7] Section 334, 21 U.S.C.

[8] Section 332, 21 U.S.C.

[9] Section 333, 21 U.S.C.

approval, or withdrawal of a previous approval, to the District Court, later changed to the Court of Appeals; the other is judicial and is intended to make effective and give strength to the requirement that "new drugs" be cleared as safe before marketing by providing the Government with certain potent judicial remedies, *available exclusively in the District Court.*

Under the 1938 Act, a new drug was one "not generally recognized by experts * * * as safe for its intended use." The Amendments added "effectiveness" as well as "safety" to the definition. Simply stated, the change effected by the Amendants was that, whereas prior to the 1962 Amendments a drug which was generally recognized as safe was not a "new drug," the Amendments defined a drug as "new" if it were not generally recognized as both safe *and effective.* Furthermore, they replaced the provision for automatic approvals of applications not disapproved within a fixed time with a requirement of a positive act of approval on the part of FDA.[10] They proceeded to provide that the Secretary must find as a basis for clearance of a new drug not only safety but "substantial evidence" of effectiveness, consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." The applicability of these amendments, including the revised definition of "new drug" to drugs already marketed, either under previously issued NDAs, or as "old drugs" requiring no FDA approval, was carefully spelt out in the Amendments and certain "grandfather rights" were granted. For all previously NDA'd drugs, the Amendments conferred a grace period of two years after the effective date of the Amendments within which to prepare evidence to satisfy the new requirement of efficacy added by the revised definition of "new drugs";

[10] Section 355(c), 21 U.S.C.

during that "transitional" period no revocation or withdrawal of approval because of a lack of substantial evidence of efficacy of such drugs was permitted.[11] For a drug, however, which on the day prior to the enactment of the Amendments was (1) being "commercially used or sold in the United States," (2) "was not a new drug as defined by" the pre-Amendment statute and (3) "was not covered by an effective (new drug application, * * *" "on the day immediately preceding the enactment date" of the Amendments, there was a permanent exemption from the efficacy provisions of the Amendments so long as the drug's labeling remained the same.[12] In summary, these provisions required that, "Those drugs which had obtained effective NDAs must be proven efficacious after two years; those which had not need never be proven efficacious so long as they had become safe prior to the 1962 Amendments." [13]

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[11] Section 107(c)(3), P.L. 87-781, Section 321, Supplement 1972, 21 U.S.C.

[12] Section 107(3)(4), P.L. 871-781, Section 321, 1972 Supplement, 21 U.S.C.; see, also, *Tyler Pharmacal Distrib. Inc.* v. *U.S. Dept.* v. *Health, E. & W.* (7th Cir. 1969) 408 F. 2d 95, 99.

It should be noted that Section 321(p)(1) provides a "grandfather clause" applicable to pre-1938 drugs. This clause is not relevant to this action, which is concerned with drugs introduced between 1938 and 1962, and the subsequent references to "grandfather clause" in this opinion are to section 107(c)(4).

[13] Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, p. 196 (1971).

See, also, *United States* v. *Allan Drug Corp.* (10th Cir. 1966) 357 F. 2d 712, 719, note 9, quoting from the Supplemental Report of the Senate Committee on Drug Amendments of 1962, as set forth in the notes to Section 321, 21 U.S.C.:

> "Thirdly, in the case of a drug on the market which was never subject to the new-drug procedure before, the amendments to the new drug definition relating to drug effectiveness would not apply to existing labeling claims."

In the Conference Report of the House Managers on the Amendments, it was stated that the Amendments included "the Senate lan-

The "grandfather clause" set forth in Section 107(c)(4) simply continues for the products satisfying its criteria the pre-1962 definition of a "new drug". Its effect is to assure that a drug which was generally recognized by qualified experts as safe for the purposes recommended for its use on October 9, 1962, need not be NDA'd as *effective* under the new requirements for the issuance of an NDA as a "new drug". But any drug, whether requiring an NDA or not, whether a "new drug" or an "old drug", is subject to the misbranding provisions of the Act and may be proceeded against on that basis. A false claim of either safety or effectiveness constitutes misbranding, rendering a drug subject to both civil and criminal penalties. *United States* v. *Article of Drug Labeled Decholin* (D.C.Mich. 1967) 264 F. Supp. 473, 482-3; *United States* v. *Lanpar Company* (D.C.Tex. 1968) 293 F. Supp. 147, 153-4.[14] Accordingly, in *United States* v. *Guardian Chemical Corporation* (2d Cir. 1969) 410 F. 2d 157, a drug manufacturer was acquitted of a charge of marketing a "new drug" without securing an NDA, but was convicted under a separate count of the indictment charging misbranding. "Thus", as one commentator has aptly stated, "the amplications of the FDA's authority (as granted by the 1962 Amendments)

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guage providing with respect to existing label claims of drugs that have never previously been subject to the new-drug procedure substantially the same savings provisions as the corresponding provision of the House bill (Section 197(d))." *U. S. Code Congressional and Administrative News*, 87th Congress, 2d Session (1962), p. 2932. Again, in H.R. Rep. # 2526, p. 23, it is stated that the exemption granted by the "grandfather clause" applies "to existing claims of drugs that have never been subject to the new-drug procedure".

[14] See, also, *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 548:

> "A good case could certainly be made that, quite apart from this, the 'efficacy' of a drug is necessarily related to the use recommended."

is (was) not due to the absence of power to proceed against ineffective drugs, but rather to authorize the exercise of that power at the initial stage, that is, *before* marketing, and also to shift the burden of proof to the applicant." Jurow, *The Effect on the Pharmaceutical Industry of the "Effectiveness" Provisions of the 1962 Drug Amendments*, 19 Food, Drug, Cosmetic Law Journal, 110, at p. 116 (1964).[15]

The plaintiffs, manufacturers of a prescription drug containing pentylenetetrazol and nicotinic acid, claim the protection of the "grandfather clause" included in Section 107(c)(4) for their products and that contention represents the substantive issue in this case. It is undisputed that plaintiffs had marketed their product commercially for many years prior to and on October 9, 1962,[16] without an NDA under the claim that it was not a "new drug" within the definition of the Act, and therefore required no NDA. Such claim was supported, it is asserted, both by previous informal advice of the Secretary and by the general recognition of the safety of such product by "experts qualified by scientific training and experience" to make such evaluation. The defend-

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[15] See, also, Senate Report # 1744, *U. S. Code Congressional and Administrative News*, 87th Cong., 2d Sess. (1962), pp. 2892 and 2893, where, in justifying the Amendments, it is stated:

> "* * * where a drug is essentially innocuous, it (FDA) must clear the drug despite the fact that its claim of effectiveness is not borne out by the evidence. In such cases the Food and Drug Administration may proceed against the drug manufacturer by seizure of the drug for misbranding. However, the Department believes that the manufacturer should satisfy the Food and Drug Administration that his product is effective for the purposes claimed before it is marketed. * * * No question of safety is involved, and the Food and Drug Administration presently has ample power, including seizure, to proceed against any safe drug for which unsupported claims of effectiveness are made."

[16] This was the day "immediately preceding the enactment date" of the Amendments of 1962.

ants, the Secretary of HEW and the Commissioner of Food and Drugs, in their brief, concede that "Over the years since 1938" and until 1968, the Food and Drug Administration had given the opinion that certain pentylenetetrazol combinations similar to those of the appellant were not "new drugs." [17] Moreover, the District Court observed in its opinion that there was "no contention (by the FDA) that the use of the plaintiffs' drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs." On this basis, the plaintiffs contended that they met exactly the criteria established for exemption from the requirements of general recognition by qualified experts of the effectiveness of their products as provided in the permanent grandfather section of the 1962 Amendments.

Prior to the filing of this action, however, the defendants withdrew their advice that products such as those distributed by the plaintiffs were "old drugs" and contended that such products did not qualify for exemption under the "grandfather clause," Section 107(c)(4). The basis for this contention was the claim (1) that these drugs were not generally recognized by qualified experts as safe as of the effective date of the Amendments of 1962 and (2) that they were "me-too" drugs, whose marketability without FDA clearance depended in turn on the NDAs granted the basic drug, and for that reason must be regarded as covered by an effective NDA on the

[17] It is, of course, axiomatic that such opinions or advice can create no estoppel against the Government. *AMP Incorporated* v. *Gardner* (D.C.N.Y. 1967) 275 F. Supp. 410, 412, n. 1, aff. 389 F. 2d 825, cert. den. 393 U. S. 825, reh. den. 395 U. S. 917. The most that can be claimed for such opinions is that they lend color and good faith to the plaintiffs' claims. FDA not only has the right but is obligated to change its opinion if it learns its prior position was erroneous. *United States* v. *60 28- Capsule Bottles, More or Less, etc.* (D.C. N.J. 1962) 211 F. Supp. 207, 215, aff. 325 F. 2d 513.

effective date of the Amendments.[18] Faced with this threat, the plaintiffs began this action for a declaratory judgment sustaining their right to exemption from proof of the effectiveness of their product and for injunctive relief awaiting the disposition of their claim for exemption. The defendants directed against the complaint a motion to dismiss or for summary judgment, which, in essence, (1) asserted primary jurisdiction in the Secretary to determine whether the products of the plaintiffs met the requirements for exemption under Section 107 (c) (4), particularly whether they were "new drugs," requiring pre-marketing approval under the Act, (2) denied the propriety of a declaratory judgment action, and (3) claimed that the products of the plaintiffs were "new

[18] The defendants assert that three "new drug" applications filed by other manufacturers and earlier approved by the FDA covered drugs similar in every particular to those marketed by the plaintiffs. Proceedings for withdrawal of the approval of such "new drugs" had been begun by FDA in advance of the filing of this action. In fact, such proceedings to a large extent prompted this action. It is the contention of the defendants that the withdrawal of what they describe as "the primary NDAs" operates to remove the marketability from what they assert are the "me-toos" or non-NDA'd drugs which are similar to other drugs which have secured effective NDAs. The plaintiffs deny that their drugs are like those previously NDA'd. They argue that those NDA'd products, unlike theirs, are intravenously administered or are a compound containing, in addition to the components of plaintiffs' drugs, reserpine. Such changes in formula or method of administering vitiated any claim by their manufacturers that they were marketing an old drug and required an approval as a new drug. The plaintiffs assert their drugs are not subject to any such disability. These, however, are questions of fact not relevant to the simple question of jurisdiction presented by this appeal and may be inquired into on remand. Even if the products of the plaintiffs be deemed "me-too" drugs (i.e., simply "a copy of a pioneer drug which preceded it on the market"), it is by no means clear that they do not "meet the requirements for section 107 (c) (4) protection" and the argument of the Government to the contrary has been described as "lacking in merit." See, Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown Law Journal, 185 at p. 203-207 (1971); Hagan, *Grandfather Protection under the Drug Amendments of 1962*, 19 Food Drug Cosmetic Law Journal, 119, at p. 125 (1964).

drugs" which did not qualify for exemption under the "grandfather clause."

The District Court sustained the right of the plaintiffs to maintain a suit for a declaratory judgment and the jurisdiction of the Court in such action to determine judicially whether the products of the plaintiffs were "new drugs," on the effective date of the Amendments, and whether they were or were not entitled to the benefits of the "grandfather clause."[19] However,—and this is the nub of the controversy between the parties on this appeal —it concluded that the Secretary had concurrent jurisdiction to determine whether plaintiffs' products were "new drugs," requiring pre-marketing clearance, and that, because of the greater expertise of the Secretary in the field, it deferred to the Secetary's assumed jurisdiction to determine whether the drugs of the plaintiffs came within the exemption provided by the "grandfather clause." It enjoined any action against the plaintiffs and their products until the plaintiffs had been accorded a hearing before the Secretary on the issue of the qualifications of these drugs for protection under the "grandfather clause." It is the conclusion of concurrent jurisdiction in the Secretary and deference to that assumed concurrent jurisdiction from which the plaintiffs have prosecuted this appeal.

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[19] In support of the right of the plaintiffs to maintain a suit for declaratory judgment, the District Court relied on *Abbott Laboratories* v. *Gardner* (1967) 387 U. S. 136 and the companion case of *Toilet Goods Assn.* v. *Gardner* (1967) 387 U.S. 158. Additional support for such right is found in *AMP, Incorporated* v. *Gardner, supra; Durovic* v. *Richardson* (D.C. Ill. 1971) 327 F. Supp. 386; *Lemmon Pharmacal Co.* v. *Richardson* (D.C. Pa. 1970) 319 F. Supp. 375. The right of the Court to determine the applicability of the "grandfather clause" is equally clear and has been sustained in *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F. Supp. 443, 445; and *United States* v. *Article Consisting of 36 Boxes, etc.* (D.C. Del. 1968) 284 F. Supp. 107, 112, n. 13, aff. 415 F.2d 369.

The defendants, on the other hand, have not cross-appealed and have accordingly acquiesced in the decision of the District Court that the action is properly maintainable as a declaratory judgment proceeding under Section 2201, 28 U.S.C. and that the District Court has jurisdiction over the substantive issue in this case, i.e., whether plaintiffs' products are "new drugs," as defined in the Act. The question in the case is thus whether the Secretary has concurrent jurisdiction to determine whether a drug is a "new drug" under the Act or whether that issue is cognizable only in the District Court. Contrary to the conclusion of the District Court, we conclude that the Act confers no such jurisdiction on the Secretary and, therefore, no basis for any deference by that Court to the concurrent jurisdiction of the Secretary.

The FDA has neither primary jurisdiction, as the defendants argue, nor concurrent jurisdiction, as the District Court concluded, to adjudicate whether a product is an old or new drug. It may, in its prosecutorial role, reach a conclusion that a product being marketed is a "new drug" requiring pre-marketing approval; but that opinion is not adjudicatory, it is only the basis on which the FDA, as the prosecutor or initiator of either a seizure or injunctive action in the District Court, may invoke the jurisdiction of that Court to determine, among other issues, whether the drug challenged is a "new drug." There is manifestly no provision in the Act for an administrative proceeding before the Secretary to compel the filing of a "new drug" application or to halt the marketing of a drug for which there is no approval by the Secretary. It is not without significance that, so far as the official reports reflect, the Secretary has never attempted directly to exercise such jurisdiction. The only occasions on which he has sought to assert such jurisdiction has been as an element in his defense to a declara-

tory judgment action.[20] Moreover, when FDA undertook its new responsibilities under the 1962 Amendments, it sought merely to review "the efficacy of *all new drugs that had been cleared*, for safety only, between 1938 and October 10, 1962" (Italics added) and enlisted the services of the National Academy of Sciences—National Research Council for this limited task. It did not assert the right to review, or assume the burden of reviewing, for efficacy, drugs such as those involved here, which had been commercially marketed on the basis of a general recognition of safety without an effective NDA as of the effective date of the 1962 Amendments. It, thus, recognized that its adjudicatory rights extended merely to the approval, or the withdrawal of approval,[22] of a drug embraced in a "new drug" application that had been approved. This confirms the conclusion that the halting of the marketing of a drug, for which there is no NDA, may not be by administrative action but must be by an injunction or *in rem* seizure proceeding, in which the Secretary appears, not in a judicial but in a prosecutorial role.[23] Those are the procedures prescribed and available to the Government under the Act.[24] The

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[20] See, *Hynson, Westcott & Dunning, Inc.* v. *Richardson* (Civ. No. 21112, D. Md., decided 9/16/70); and *Ciba Corp.* v. *Richardson* (Civ. No. 1210-70, D. N.J., decided 3/10/71); but c.f., *Lemmon Pharmacal, supra.*

[21] See *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F.2d 536, 539, and 31 F.R. 9426.

[22] The authority of the Secretary to withdraw an approval of any "new drug" application filed under the Act of 1938 after hearing is specifically granted by Section 355(e), 21 U.S.C.

[23] Of course, in a proper case the Government may also institute criminal proceedings in the District Court. See Section 333, 21 U.S.C.

[24] Cf. *United States* v. *Allan Drug Corporation* (10th Cir. 1966) 357 F.2d 713, 718, cert. den. 385 U. S. 899, in which the Secretary is quoted to the effect that, " 'As to drugs already on the market that have never been subject to the new-drug procedure but are not generally recognized as effective, the burden remains on the

Secretary, it is true, has offered to provide "advice" on whether a product meets the qualification of an old drug but he categorizes his action in such instances as merely "advice" and makes no claim of finality therefor. Nor is there, as we have already observed, any provision for judicial review of such "advice".[25] The only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of an approval, of a "new drug" application.[26] That this is so follows from the limitations placed by the Act on judicial review of the decisions of the Secretary. The Secretary himself asserted, shortly after the enactment of the 1962 Amendments, in *Turkel* v. *Food and Drug Administration, Dept. of H.E.W., supra,* at p. 845, that the Act "grants a right to appeal only from an order of the Food and Drug Administration approving or disapproving a New Drug Application". In keeping with the Secretary's contention as to the extent of his adjudicatory powers, the Court in that case held that the right of appeal from an order of the Secretary "applies only to an order of the Secretary refusing or withdrawing approval of an application for sale and distribution of a new drug" (at pp. 845-6). It is not to be assumed that the Act confers an adjudicatory right on the Secretary from which no judicial review, however limited, is provided or allowed. Yet this is the usual situation that would be presented if the Secretary were held to have jurisdiction to ad-

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Government to prove *in court*, insofar as unchanged labeling claims are concerned, they do not have their claimed effect. If the labeling claims are changed, however, these must be approved under the new-drug procedure.'" (Italics added.)

[25] See *Turkel* v. *Food and Drug Administration, Dept. of H.E.W.* (6th Cir. 1964) 334 F.2d 844, 846, cert. denied 379 U. S. 990, rehearing denied 380 U. S. 927: "The jurisdiction of the United States Courts of Appeal to review administrative acts of federal agencies is wholly dependent upon statute."

[26] Section 355(b), 21 U.S.C.

judicate whether a drug meets the statutory criteria of a "new drug".[27]

The District Court, in finding concurrent jurisdiction, held that "This grant of authority to approve or withhold approval of new drug application, * * * necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which required an approved new drug application for lawful interstate shipment." This reasoning assumes that an application for approval by the Secretary under the Act poses as its initial issue whether the product is a new drug. No such issue is posed by the application. The very filing of the application is a concession and recognition by the applicant-manufacturer that the article is a "new drug"; otherwise, there would be no reason to file the application. As a matter of fact, in the prescribed form of application, the applicant describes his product as "a new drug". 21 C.F.R. 130.4. The applicant makes the determination whether his product is a "new drug" and whether he must file for pre-marketing clearance by the Secretary. And when filed, the application puts in issue only one question: Is the article safe and effective? That and that alone is the issue to be considered by the Secretary in connection with an application for approval filed by a manufacturer under Section 355(d), 21 U.S.C. That issue is quite different from that presented when there is an issue whether a drug fits the statutory definition of "new drug" in the Act. The criterion for ascertaining whether a product is within the statutory definition of "new drug" under the Act is not safety and effectiveness *per se*, which, as we have observed, is the issued before the Secretary in connection with application for approval of a "new drug", but "whether the government has shown by a preponderance of the

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[27] Cf., *Abbott Laboratories* v. *Gardner* (1967) 387 U. S. 136, at p. 140.

evidence that the 'drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof." [28] That is an issue that must be and is resolved, sometimes with, and at other times without a jury, in practically every injunctive, seizure, or criminal proceeding under the Act. See, for instance, *United States* v. *Articles of Drug Labeled "Quick-O-Ver"*, *supra; United States* v. *41 Cases, More or Less* (5th Cir. 1970) 420 F.2d 1126, 1128; *United States* v. *Article of Drug, etc., supra*, at p. 392; *United States* v. *Article . . . Consist. of 216 Carton* (2d Cir. 1969) 409 F.2d 734, 742; *United States Article Consisting of 36 Boxes, etc., supra*, at p. 113; see, also, *United States* v. *Article of Drug, etc.* (D.C. Md. 1971) 331 F. Supp. 912, 915-7. That was one of the issues resolved in the declaratory action of *Lemmon Pharmacal Co.* v. *Richardson, supra.*[29] It is

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[28] *United States* v. *Articles of Drug Labeled "Quick-O-Ver"*, *supra*, at pp. 45-6.

See, also:

AMP, Incorporated v. *Gardner, supra*, at p. 831:

"But the safety of the products is not what is at issue here. The question is whether there is general recognition among qualified experts of the products' safety and effectiveness—if there is not, the products must be submitted to the Secretary of Health, Education and Welfare for a determination as to safety, adequacy of testing, etc."

United States v. *Article of Drug, etc.* (5th Cir. 1969) 415 F.2d 390, 392:

"Both sides agree that the nature of expert opinion about Furestrol, and not its actual safety or effectiveness, is the ultimate fact issue."

Cf., *United States* v. *Seven Cartons, More or Less, etc.* (7th Cir. 1970) 424 F.2d 1364, 1365.

[29] In discussing this case, the commentator in 60 Georgetown Law Journal, p. 199, note 87, says:

[Footnote continued on page 44a]

manifestly a justiciable issue and the plaintiffs are entitled to a judgment on that issue by the Court, which alone has the jurisdiction to resolve it. In the absence of any statutory review proceedings within which they may assert their claim of exemption, the plaintiffs are not to be compelled to proceed at their peril, subject to the possibility of both civil and criminal penalties, but are entitled to seek relief by way of a declaratory judgment action. The District Court should accordingly have retained jurisdiction and proceeded to determine whether the plaintiffs' drugs met the criteria for exemption under Section 107(c)(4). We deem it premature for us to consider at this stage whether plaintiffs' products meet such criteria. That issue was not developed in the record before, or ruled on by, the District Court.[30] Upon remand, the issue can be considered by the Court in the light of the record that may be made by the parties.

REMANDED, WITH DIRECTIONS.

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[29] [Continued]

"In *Lemmon Pharmacal*, the Court, while noting that determining safety and efficacy would normally be within the primary jurisdiction of the agency, concluded that the question of section 107(c)(4) protection was properly before it."

[30] See *United States* v. *Article Consisting of 36 Boxes etc.*, *supra*, at p .113.

APPENDIX C(2)

UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 71-1596

USV PHARMACEUTICAL CORPORATION,
Appellee,

—versus—

ELLIOT L. RICHARDSON, Secretary of Health, Education, and Welfare, and HERBERT L. LEY, JR., Commissioner of Food and Drugs, Food and Drug Administration,
Appellants.

Appeal from the United States District Court for the Eastern District of Virginia, at Alexandria. Oren R. Lewis, District Judge.

(Argued December 8, 1971. Decided May 24, 1972.)

Before WINTER, RUSSELL and FIELD, Circuit Judges.

RUSSELL, CIRCUIT JUDGE:

Unlike the drug manufacturers in *Bentex*,[1] this plaintiff markets a line of citrus bioflavonoid drugs,[2] of

[1] *Bentex Pharmaceuticals, Inc.* v. *Richardson*, No. 71-1243 (4th Cir., appeal docketed March 11, 1971).

[2] "Bioflavonoid" is defined in Dorland's Illustrated Medical Dictionary, 2d Edition, as follows: "a generic term for a group of compounds which are widely distributed in plants and animals and which are concerned with maintenance of a normal state of the walls of small blood vessels." Stipulation of Facts, # 4.

which all but two were covered by NDAs issued at various times in 1955 and 1956. Like the plaintiffs in *Bentex*, however, it seeks by an action for declaratory judgment to secure the benefit of the exemption available under the "grandfather clause" [a] from the enlarged definition of a "new drug" included in the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act of 1938. The defendants, who are the Secretary of Health, Education and Welfare (hereinafter referred to as HEW) and the Commissioner of the Food and Drug Administration (hereafter referred to as Commissioner), urge that jurisdiction should be refused on two grounds: 1. Primary jurisdiction lies with HEW; and 2. Failure to exhaust administrative remedies. They, also, attack the right of the plaintiff to claim the exemption. The District Court sustained jurisdiction and, largely on the basis of a Stipulation of Facts, upheld plaintiff's right to the statutory exemption both for its NDA'd and its non-NDA'd drugs. We reverse.

The threshold question raised by the defendants and overruled by the District Court may be quickly disposed of. Under similar circumstances in *Bentex*, we sustained the right of the District Court to entertain an action for declaratory judgment. We reach the same result here. Since we dismiss the claim of the plaintiff for exemption on behalf of its drugs on substantive grounds, it is unnecessary to consider the additional objection that plaintiff has failed to exhaust administrative remedies.

The substantive issue posed by this action is the right of the plaintiff to the exemption provided by section 107(c)(4) from the revised definition of "new drug" incorporated in the 1962 Amendments. In resolving that issue, we must differentiate, even as the "grandfather

[a] Section 107(c)(4), Pub. L. 87-781 (1962), 21 U.S.C., 1972 Supplement, pp. 191-2.

clause" itself does, between the plaintiff's drugs, which were covered by an "effective NDA",[4] and those, which were marketed without an NDA. The Act makes a distinction in "grandfather" rights between a drug marketed under an NDA[5] and one marketed without an NDA. In the case of a drug covered by a previously approved NDA, the 1962 Amendments required the Secretary to withdraw NDAs if after notice and opportunity of hearing, the applicant failed to file substantial evidence[6] that the drug previously approved is both safe and effective.[7] For such drugs, however, a grace period or temporary "grandfather right" was granted. Under it, the manufacturer was given two years within which to develop his showing of effectiveness and, during this period, the Secretary was prohibited from withdrawing or suspending the previously granted NDA.[8] On the other hand, a non-NDA'd drug which met the criteria stated in section 107(c)(4) was exempted permanently from the amended definition of "new drug" made by the 1962 Amendments and was thereby relieved of securing an approved NDA as a condition for marketing clearance. The statutory criteria for this permanent "grandfather" exemption are stated as "any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined in section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act".

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[4] "Effective", as used in this phrase, means simply approved. Hagan, *Grandfather Protection Under the Drug Amendments of 1962*, 19 Food Drug Cosm. L. J., 119, p. 121.

[5] This is the term used to describe an approved pre-clearance application under Section 355.

[6] "Substantial evidence" is defined in the Act (21 U.S.C. 355(d)).

[7] Section 355(e), 21 U.S.C.

[8] Section 107(c)(3)(B), 21 U.S.C., note foll. Section 321.

It is the contention of the plaintiff that all its drugs in question, both those previously NDA'd and those not, are protected by the permanent "grandfather clause" (i.e., Section 107(c)(4)). Because the statute seemingly makes a distinction between the two, it is proper to consider separately the two groups of drugs: i.e., those having NDAs and those without NDAs.

Taking up first plaintiff's NAD'd drugs: There is no dispute that such drugs met criteria (A) and (B), as set forth in the "grandfather clause", but the defendants seriously dispute the claim that they meet condition (C). Facially at least, this contention of the defendants seems unanswerable. These drugs are "covered by an effective application" or NDA, and are thus specifically barred by condition (C) from qualifying for exemption from the application of the effectiveness Amendments of 1962. The District Court found, however, that before "the day immediately preceding the enactment date", which was October 9, 1962, the previously granted NDAs had been effectively and practically withdrawn and that accordingly the drugs were not covered by an effective NDA on the crucial date of October 9, 1962. The error in this reasoning, however, is that it assumes that a manufacturer may effect a withdrawal of an effective NDA, either by a formal notice or by discontinuing compliance with the reporting requirements for NDA'd drugs. While an applicant may, during the pendency of his application, withdraw his application, he has no such right after approval of the application by the Secretary. At that point only the Secretary can withdraw the approval. As one commentator has accurately summed up, "It is true that a manufacturer may withdraw a pending NDA. Sec. 21 C.F.R. sec. 130.8 (1971). However, no provision in the law permits a manufacturer to withdraw an effective NDA; only the FDA can do so through Section 505(e) procedure".* Prior to October 9, 1962, there was

* Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185 at p. 198, n. 77 (1971).

in this case no proceeding by FDA under Section 505(e) with reference to plaintiff's NDA'd drugs and there was accordingly no valid withdrawal of the plaintiff's effective NDAs, on or before the enactment date of the 1962 Amendments.

The plaintiff, through, presses another theory upon the basis of which it claims the previously issued NDAs are to be regarded as ineffective on October 9, 1962. Thus it argues that its pre-1962 NDA'd drugs became generally recognized as safe on or before October 9, 1962. So much the defendants seem to concede in the Stipulation of Facts submitted to the District Court. From this fact, it reasons that its NDA drugs ceased to be "new drugs" as defined in the Act, on or before October 9, 1962, and, ergo, its previously issued NDAs were no longer needed or "effective" on the critical date of October 9.[10] The difficulty with this argument, plausible thought it may be, is that it would make surplusage of requirement (C) in the statute. Thus, if a drug met the test set up in (B), that is, was generally recognized as safe on October 9, 1962, it would not be necessary, under the plaintiff's argument, to consider whether (C) was applicable or not. Such a construction of the exemption statute, under which a clearly stated condition to its application is to treated as a nullity, offends the well-settled rule of statutory construction that all parts of a statute are to be given effect if at all possible.[11] It is manifestly possible to give effect to the conditions enunciated in both (B) and (C). There are many drugs that satisfy both conditions, that is, are generally recognized as safe and effective and are being marketed without an approved NDA. There is nothing inconsistent in the two require-

[10] See Barth, *Following the NAS-NRC Effectiveness Review, What?*, 22 Business Lawyer, 1185, 1187 (1967).

[11] *Jarecki* v. *G. D. Searle & Co.* (1961) 367 U.S. 303, 307; *Ginsberg & Sons* v. *Popkin* (1932) 285 U.S. 204, 208.

ments. Moreover, condition (C) represented a limitation on the right to an exemption that the Congress clearly and unmistakably intended to apply. The Congress never intended that a drug being marketed under an approved NDA might qualify under the "grandfather clause." This is plain from the comment in the Conference Committee Report that the exemption was to apply "to existing labeling claims of drugs *that have never previously been subject to the new-drug procedure*". (Italics added.) H.R. Rep. 2526, 87th Cong., 2d Sess., p. 23. Moreover, the argument of the plaintiff would run counter to the principle that statutory exemptions, particularly as applied to statutes concerned with public health and safety, are to be strictly and narrowly construed.[12]

The plaintiff has, however, two drugs,[13] involved in this proceeding, which were generally recognized as safe and were [14] marketed as "old drugs" without an approved NDA on October 9, 1962. These drugs, as we earlier indicated, present separate problems from those drugs for which there are approved NDAs. They fall into the category of what are generally described in the trade as "me-too" drugs.[15] Such a drug, if generally regarded as safe on October 9, 1962, meets literally the criteria for exemption stated in the "grandfather clause". To sustain the exemption, however, creates an inequitable result, provided the pioneer drug was NDA'd. In that event, the pioneer drug would be subject to withdrawal of marketing privilege absent substantial evidence of effec-

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[12] *United States* v. *Allan Drug Corporation* (10th Cir. 1966) 357 F.2d 713, 718, cert. denied 385 U.S. 899.

[13] Duo-C.V.P. with Vitamin K Capsules and Bivam.

[14] Stipulation of Facts, Number 17.

[15] A "me-too" drug is generally defined as "one which is equivalent to another, pioneer drug, which preceeded it on the market." Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 198, n. 78, (1971).

tiveness, whereas its copy would enjoy immunity from any such requirement under Section 107(c)(4). Most commentators, while admitting the incongruity of this result, justify it as one compelled by the literal language of the statute.[16] Their reasoning is similar to that of the Court in *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 542, where speaking to a somewhat illogical provision in this same Act, Judge Friendly said: "A sufficient answer is the simple if not altogether satisfying one that Congress said so."[17] The FDA itself has recognized the vexing problem presented by the "me-too" drug and has sought to resolve it by a change in its position on the scope and application of an NDA.

It is the contention of the FDA that an approved NDA covers not merely the marketing of the parent but also its "me-too" offsprings and for that reason the "me-too" drugs have been permitted to be marketed without an NDA. Accordingly, under this theory, the withdrawal of the approved NDA of the pioneer operates as a withdrawal of marketing rights for the "me-too", unless the latter, either individually or in conjunction with its pioneer, provides substantial evidence of effectiveness. This view has, however, been severely criticized and with considerable reason. It is, as one critic has observed, "at variance with the uniform position it (FDA)

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[16] See, Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 203 (1971):

> "Surely, me-too drugs never processed through the new drug procedures satisfy all the requirements of section 107(c)(4)."

To the same effect is Hagan, *Grandfather Protection Under the Drug Amendments of 1962*, 19 Food Drug Cosm. L.J., 119, at pp. 125-6; *D'Andrade, The Effect of NAS-NRC Review on Me-Too and Post-'62 Drugs*, 25 Food, Drug, Cosm. L.J., 330, 334 (1970).

[17] This, of course, is not the only inequity in the Amendments. There are other inequities, as FDA freely conceded at a House Hearing before a Subcommittee of the Commission on Government Operations on Drug Efficacy, Part 2, 91st Con., 1st Sess. (1969), pp. 384-5.

has taken over the years with regard to the nature of NDAs." This position, which is termed the "personal approach" holds that "Section 505 applies to drugs as individual articles, not as collective groups, and that each manufacturer of a new drug must file his own NDA." This critic concludes with the observation that it is "an unjustifiable exercise in semantics to say that a drug legally marketed without an NDA was 'covered' by the NDA of another manufacturer's drug." [18]

That the policy of FDA has heretofore been contrary to the position now taken by it is further illustrated by the circumstances under which at least one of the "me-toos" of the plaintiff began marketing. Prior to marketing Bivam, one of its "me-toos" similar in formula to other drugs previously NDA'd by it, the plaintiff inquired of FDA whether it was an "old drug" entitled to be marketed without an NDA. FDA, after reviewing its composition and labeling, advised the plaintiff it was a product "generally regarded as safe" (and thus an "old drug") and could be marketed without an NDA. There was no suggestion by the plaintiff that it sought to market this drug under any previous NDA granted one of its products nor did the FDA base its advice on that basis. Both the plaintiff and FDA assumed at that time that a "me-too" drug, which had become generally recognized as safe, was entitled to be marketed without an NDA; in short, that the qualification for marketing a "me-too" drug was general recognition of safety and not the NDA of its pioneer.

It would seem that the consistent construction of the Act by the FDA for thirty years [19] and a construction

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[18] Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 203, n. 111 (1971).

[19] See, Hagan, *supra*, at p. 125:

> "Furthermore, the concept that new drug clearance by one manufacturer affects the rights of subsequent manufacturers

which accords with the literal language of the Act itself may only be changed by Congress itself.[20] In fact, the General Counsel of FDA, in testimony before a House Subcommittee Hearing on Drug Efficacy, Part 2 (91st Cong., 1st Sess., 1969) p. 375, expressed the wish that Congress would "pass" a clarifying amendment on this issue, conceding that the position of his agency was in considerable doubt.

But even if it be assumed that "me-too" drugs are generally entitled to section 107(c)(4) protection, provided they were generally recognized as safe on October 9, 1962, that does not resolve the right of the plaintiff's "me-toos" to exemption. As has been pointed out, the reasoning on which "me-toos" are regarded as not covered by the NDAs granted the manufacturers of their pioneers is that an NDA is regarded as "personal" to the manufacturer submitting the application and to the drug covered. But in this case, the "me-toos" are similar in formula and labeling to other drugs for which the plaintiff itself applied and obtained NDAs. It is true that, in the case of one drug at least, to which reference has already been made, plaintiff's "me-toos" were regarded as exempt, not because plaintiff had an approved NDA for a similar drug, but because FDA was of the opinion that it met the requirements for classification as an old drug. Nonetheless, it is the "per-

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is inconsistent with the established doctrine that new drug clearance is *personal* to the applicant, and does not embrace the drug *per se*."

[20] Cf., comment in Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal 185, at pp. 206-7 (1971):

"Ultimately the issue of the status of me-too drugs will have to be squarely faced, and the FDA interpretation of section 107 (c)(4), holding that they follow the pioneer's fate, should be repudiated by the courts. In that event the agency will undoubtedly ask Congress for new legislation to remedy the situation. In view of the obvious inequities in the present situation, this would seem to be the most desirable solution."

sonal" character of the NDA that has been deemed as the basis on which it is contended that the "me-toos" are not covered by the NDA granted another manufacturer, albeit the drugs involved may be similar. That reasoning manifestly cannot sustain a right of exemption in favor of plaintiff's "me-toos". The plaintiff's NDAs, being "personal" to it, would cover all its products similar in formula, including those specifically described in its applications and all others like in formula. The similarity in formula, between plaintiff's NDA'd drugs and its "me-toos" is stipulated. Under those circumstances, both the NDA'd and the "me-too" drugs will be treated alike and neither can qualify for exemption under the terms of section 107(c)(4). It is recognized that this conclusion places the plaintiff in a less favorable position than that occupied by others who may have copied its product prior to October 9, 1962. That inequity is, however, inherent in the law and may only be redressed by Congress, not by the Courts under the guise of construction.

Reversed, with directions to enter judgment for the defendants.

REVERSED.

APPENDIX D

Conflicting Opinion

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 71-1512

CIBA CORPORATION, a corporation of the State of Delaware,

Appellant,

v.

ELLIOTT L. RICHARDSON, Secretary of Health, Education & Welfare, and DR. CHARLES C. EDWARDS, Commissioner of Food and Drugs.

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Argued April 11, 1972
Before HASTE, VAN DUSEN and ALDISERT, *Circuit Judges*

OPINION OF THE COURT
(Filed June 5, 1972)

PER CURIAM:

Ciba Corporation has taken this appeal from an order of the District Court for the District of New Jersey dismissing a complaint in which Ciba sought a declaratory determination that its drug product, Ritonic Capsules, is exempt from the requirement of 1962 amendments of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355,

that new drugs be excluded from the market unless proven effective as claimed for them. The complaint also sought an injunction against the implementation of an administrative order, entered by the Commissioner of Food and Drugs after notice and opportunity for an evidentiary hearing, that withdrew approval of the drug upon the basis of a finding that the manufacturer's claims as to its effectiveness were unproven. On appeal, the Court of Appeals for the Second Circuit has affirmed that order. *Ciba-Geigy Corp.* v. *Richardson*, 1971, 446 F.2d 466. That affirmance occurred after the district court had dismissed the present suit and is subject to review by the Supreme Court.

The appellant's basic position seems to be that neither the Commissioner in an administrative proceeding under § 355(e) to determine whether lack of effectiveness as claimed makes a drug unmarketable, nor a court of appeals in reviewing the administrative decision, has jurisdiction to decide as to threshold question whether the product in controversy is a "new drug" within the meaning of the statute, § 355, that covers "new drug" applications and administrative proceedings pursuant thereto. We find no merit in that argument. Inherent in the grant of administrative competency to conduct and decide new drug proceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such a proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision.

In disapproving Ritonic Capsules the Commissioner and the Court of Appeals for the Second Circuit necessarily decided that the 1962 amendments of the Act were applicable to that product. That determination is reviewable by the Supreme Court. It is neither necessary nor appropriate that the District Court for the District of

New Jersey entertain a separate suit by the loser in the administrative proceeding and in the direct appeal therefrom for a redetermination of the same question.

The judgment will be affirmed.

A True Copy:
Teste:

Clerk of the United States Court of Appeals for the Third Circuit.

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FILED

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MICHAEL RODAK, JR., CLERK

IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-528

CIBA CORPORATION, a corporation of the State of Delaware,
Petitioner,

vs.

ELLIOTT L. RICHARDSON, Secretary of Health, Education & Welfare and DR. CHARLES C. EDWARDS, Commissioner of Food and Drugs,
Respondents.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. .....

CIBA CORPORATION, a corporation of the State of Delaware,

Petitioner,

vs.

ELLIOTT L. RICHARDSON, Secretary of Health, Education & Welfare and DR. CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Respondents.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

Opinions Below

The opinion of the Court of Appeals appears at —— F. 2d ——, CCH Food Drug and Cosmetic Law Reporter ¶40,676 (3rd Cir. 1972) and in the appendix hereto, *infra*, at 9a. The oral opinion of the District Court did not consider the issues raised herein and, by stipulation of the parties, has not been reprinted.

Jurisdiction

The judgment and opinion of the Court of Appeals were entered on June 5, 1972. By order signed by Justice Rehnquist of this Court dated September 1, 1972, the time for filing a petition for a writ of certiorari herein was extended to October 2, 1972. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

Question Presented

Do the Federal district courts have exclusive jurisdiction to adjudicate whether a drug is a "new drug" as defined in the Food, Drug and Cosmetic Act of 1938, as amended, and therefore subject to the regulatory proceedings applicable to such drugs?

Statute Involved

The statute involved is The Food Drug and Cosmetic Act of 1938, as amended, 21 U.S.C. § 301 *et seq.* The pertinent sections of that Act are set forth in the appendix hereto, *infra,* at p. 1a *et seq.*

Statement of the Case

The Federal Food, Drug and Cosmetic Act of 1938,[1] as amended (the "Act"), provides that certain drugs called "new drugs" may not be shipped in interstate commerce without prior, formal Food and Drug Administration (the "FDA") approval granted on the basis of information submitted as part of a New Drug Application. A New Drug Application for Ritonic, the drug which is the subject of this action, became effective on January 12, 1958. At that time, the Act required such Applications to contain evidence demonstrating that the drug was *actually* safe for the conditions of use recommended or prescribed in its

[1] 21 U.S.C. § 301 *et seq.*

labeling. The Act also provided at that time that a drug was not a "new drug" if it was *generally recognized* as safe for the conditions of use recommended or prescribed in its labeling.

In 1962 the Act was amended[2] so as to, *inter alia*, make approval of a New Drug Application dependent upon the production of specified evidence of effectiveness as well as safety. In addition, the definition of a "new drug" was expanded to also include drugs not generally recognized as effective. As a result of these amendments, the FDA contracted with the National Academy of Sciences-National Research Council (the "NAS-NRC" for the review of drugs subject to New Drug Applications prior to 1962 to determine whether there existed for such drugs the requisite evidence of their effectiveness.

On September 30, 1970, after an exchange of several communication between Ciba and the FDA, the FDA published in the Federal Register a notice[3] denying Ciba's request for a hearing and withdrawing, based on a finding by an NAS-NRC panel of a lack of the requisite evidence of effectiveness, the New Drug Application previously in effect for Ritonic.

In response to the FDA's withdrawal of the New Drug Application for Ritonic, Ciba filed this action seeking a declaration that Ritonic is not a "new drug" and therefore legally marketable without an approved New Drug Application.[4]

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[2] 76 Stat. 780 (1962)

[3] Vol. 35, No. 190

[4] Ciba also filed a direct appeal under § 505(h) of the Act from that portion of the FDA's order refusing Ciba's request for an administrative hearing to review the adequacy of the evidence submitted in support of the New Drug Application for Ritonic, and the denial of a hearing was affirmed. *Ciba-Geigy Corporation* v. *Richardson*, 446 F. 2d 466 (2nd Cir. 1971). The Second Circuit action did not in any way consider and, for the reasons indicated hereinafter, could not have considered the "new drug" status of Ritonic.

Respondents moved to dismiss the complaint on the ground, *inter alia*, that the FDA, not the courts, has exclusive jurisdiction to determine whether a drug is a "new drug" and that a manufacturer's only avenue of judicial redress from an FDA determination on this point is by way of appeal to a circuit court of appeals. By stipulation of the parties, this jurisdictional question was the sole issue briefed or argued in either of the courts below.

The district court held the jurisdictional issue to be moot and dismissed the action on the ground that even if the court had jurisdiction it would exercise its discretion and refuse to determine whether Ritonic was a "new drug" in a declaratory judgment action. The Third Circuit Court of Appeals affirmed the dismissal on the ground that the FDA has jurisdiction to adjudicate whether a drug is a "new drug" and that the FDA properly exercised that jurisdiction in its administrative proceeding withdrawing the New Drug Application previously in effect for Ritonic.

Ciba seeks a writ of certiorari to establish that, under the Act, the district courts have exclusive jurisdiction to determine whether a particular drug is a "new drug" and therefore subject to the "new drug" procedures.

Reasons for Granting the Writ

The Act provides that before a manufacturer may ship a "new drug" in interstate commerce it must obtain FDA approval of a New Drug Application for that drug.[5] The FDA is instructed to issue an order denying approval of a New Drug Application[6] or withdrawing approval previously granted[7] if the Commissioner concludes that there is a lack of "substantial evidence" that the drug involved is

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[5] Act § 301(d) which incorporates by reference § 505(a); 21 U.S.C. 331(d), 355(a); Appendix pps. 1a, 3a

[6] Act § 505(d); 21 U.S.C. 335(d); Appendix p. 3a

[7] Act § 505(e); 21 U.S.C. 355(e); Appendix p. 4a

safe and effective for the conditions of use prescribed or recommended in its labeling.

"Substantial evidence" is a term of art defined in the Act and the regulations promulgated thereunder[8] as, in essence, the results of "adequate and well-controlled clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have . . . [in its labeling.]"

Not all drugs, however, are required to have an approved New Drug Application before they can be marketed; only "new drugs" must follow this procedure. The term "new drug" is also a term of art defined in the Act.[9] In essence a "new drug" is any drug which is not generally recognized by experts qualified to evaluate the safety and effectiveness of drugs as being safe and effective for the conditions of use recommended in its labeling or any drug which is so recognized but which has not been used to a material extent or for a material time for the conditions recommended in its labeling.

The distinction between whether a drug is a "new drug", *i.e.*, generally recognized as safe and effective, and not required to have a New Drug Application, and whether a "new drug" has been demonstrated by "substantial evidence" to be safe and effective and therefore entitled to approval of its New Drug Application is part of the basic structure of the Act. If a drug has been in use by the medical profession for a material time and to a material extent and if, through such use, has become generally recognized as being safe and effective, then the drug is no longer a "new drug" and the manufacturer may market it

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[8] Act § 505(d); 21 U.S.C. 355(d); Appendix p. 3a; 21 CFR, Part 130, § 130.12

[9] Act § 201(p); 21 U.S.C. 321(p); Appendix p. 1a

without it being the subject of an approved New Drug Application.

Respondents do not dispute that drugs which are not "new drugs" may be legally marketed without an approved New Drug Application; they argue, rather, that the FDA rather than the district courts has jurisdiction of the "new drug" question and that when the FDA has made a determination of this question with respect to a particular drug the only judicial remedy is an appeal from the FDA's action to an appropriate court of appeals.

The court below, without citation of authority, accepted the position of the respondents. It did so by concluding that the FDA's jurisdiction to determine whether a drug is a "new drug" is implicit in that agency's jurisdiction to determine whether a "new drug" is entitled to New Drug Application approval. That conclusion is not only devoid of judicial support but also is without cited statutory authority.

Administrative agencies cannot restrict the rights of those regulated unless such jurisdiction or authority is expressly conferred by statute. Section 505 of the Act establishes the power in the FDA to regulate "new drugs". Nowhere in that section, or in any other section of the Act, is the agency authorized to adjudicate the issue of whether a drug or is not a "new drug". The procedure established in Section 505 of the Act contemplates only the adjudication of whether the tests for approval of a New Drug Application, *i.e.* "substantial evidence" of safety and effectiveness, have been met.

In sharp contrast to the conclusion of the court below, the Court of Appeals for the Fourth Circuit, in *Bentex Pharmaceuticals, Inc.* v. *Richardson,* —— F. 2d ——, CCH Food Drug and Cosmetic Law Reporter ¶ 40,665 (4th Cir. 1972), appendix hereto, *infra,* p. 11a, rejected the argu-

ment of the FDA advanced below and concluded that the FDA was without jurisdiction to determine whether a drug is a "new drug"[10].

The *Bentex* case, like the instant one, was a declaratory judgment action commenced by a manufacturer seeking a determination that its product was not a "new drug". The manufacturer in *Bentex*, like Ciba, acted after receiving notice from the FDA that it had determined its product to be a "new drug" which lacked an approved New Drug Application and that consequently the FDA would institute enforcement proceedings if the drug was not withdrawn from the market. In *Bentex* the FDA argued, as it did below, that the district courts lack jurisdiction to adjudicate the "new drug" status of drugs

The Fourth Circuit concluded that the questions of whether to grant approval of a New Drug Application and whether a drug is a "new drug" are wholly separate and distinct. After an analysis of the Act, it held that there was no basis for concluding that the FDA had jurisdiction to adjudicate the latter question or that the Court of Appeals would have jurisdiction on appeal to review such a determination if it were made.

This conclusion of the Fourth Circuit is consistent with the historic position of the FDA. As that court noted, the FDA has not, until recent times, ever claimed jurisdiction to determine the issue of whether a product is or is not a "new drug".

The conflict in the circuits on the jurisdictional issue is one which should be promptly resolved by this Court. The determination of whether a drug is a "new drug" or not is ofttimes determinative of whether a manufacturer may continue to market the product. The economic impact of this issue is thus obvious.

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[10] See also *USV Pharmaceuticals Corp.* v. *Richardson*, 461 F. 2d 223 (4th Cir. 1972)

The efficient administration of one of the nation's most important regulatory acts has, as a result of the conflict in the circuit opinions, been substantially impaired. Is it for the FDA to adjudicate whether a drug is a "new drug"? If so, as the Third Circuit concludes, that adjudication will take place in a forum where the FDA acts both as prosecutor and judge. It is submitted that there is no basis for that conclusion, and that that issue, as held by the Fourth Circuit, is one which is to be decided in an impartial judicial forum. That result is supported not only by the provisions of the Act but also by the substantial body of law developed in the district courts since the passage of the Act. See *e.g.*, *Merritt Corp.* v. *Folsom*, 165 F. Supp. 418 (D.D.C. 1958); *U.S.* v. *354 Bulk Cartons* • • • *"Trim Reducing Aid Cigarettes"*, 178 F. Supp. 847 (D.N.J. 1959); *U.S.* v. *An Article of Drug . . . Quinaglute*, 268 F. Supp. 245 (E.D.Mo. 1967); *U.S.* v. *Articles of Drug . . . Quick-O-Ver*, 274 F. Supp. 443, 445-46 (D.Md. 1967); *U.S.* v. *An Article of Drug . . . "Line Away"*, 284 F. Supp. 107 (D. Del. 1968) affirmed other grounds 415 F.2d 369 (3rd Cir. 1969); *U.S.* v. *7 Cartons . . . "Ferro-Lac"*, 293 F. Supp. 660 (S.D. Ill. 1968) affirmed 424 F. 2d 1364 (7th Cir. 1970); *U.S.* v. *An Article of Drug . . . "Furestrol"*, 294 F. Supp. 1307 (D. Ga. 1968) affirmed 415 F.2d 390 (5th Cir. 1969); *U.S.* v. *An Article of Drug . . . Excedrin P.M.*, —— F. Supp. ——, CCH, Food Drug and Cosmetic Law Reporter ¶ 40,486 (E.D.N.Y. 1971). See also *U.S.* v. *Allan Drug Corp.*, 357 F.2d 713 (10th Cir. 1966).

Conclusion

For the foregoing reasons it is respectfully submitted that the writ of certiorari requested hereby should be issued and the opinion and judgment of the Third Circuit Court of Appeals reversed.

Respectfully submitted,

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Date: September 29, 1972

Of Counsel:

PITNEY, HARDIN & KIPP
MICHAEL E. RODGERS

APPENDIX

Text of Pertinent Sections of the Food, Drug and Cosmetic Act.

Act § 201(p), 21 U.S.C. 321(p)

"(p) The term 'new drug' means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a 'new drug' if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."

Act § 301(d); 21 U.S.C. 331(d)

"Sec. 301. The following acts and the causing thereof are hereby prohibited:

* * *

Text of Pertinent Sections of the Food, Drug and Cosmetic Act.

(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 404 or 505."

Act § 302(a); 21 U.S.C. 332(a)

"Sec. 302. (a) The district courts of the United States and the United States courts of the Territories shall have jurisdiction, for cause shown, and subject to the provisions of section 17 (relating to notice to opposite party) of the Act entitled 'An Act to supplement existing laws against unlawful restraints and monopolies and for other purposes', approved October 15, 1914, as amended (U.S.C. 1934 ed., title 28, sec. 381), to restrain violations of section 301, except paragraphs (h), (i) and (j)."

Act § 303(a); 21 U.S.C. 333(a)

"Sec. 303. (a) Any person who violates a provision of section 301 (other than a provision referred to in subsection (b) of this section) shall be imprisoned for not more than one year or fined not more than $1,000, or both; except that if any person commits such a violation after a conviction of him under this subsection has become final, or commits such a violation with the intent to defraud or mislead, such person shall be imprisoned for not more than three years or fined not more than $10,000, or both."

Act § 304(a)(1); 21 U.S.C. 334(a)(1)

"Sec. 304. (a)(1) Any article of food, drug, device, or cosmetic that is adulterated or misbranded when introduced into or a while in interstate commerce or while held for sale (whether or not the first sale) after shipment in interstate commerce, or which may not,

under the provisions of section 404 or 505, be introduced into interstate commerce, shall be liable to be proceeded against while in interstate commerce, or at any time thereafter, on libel of information and condemned in any district court of the United States 'or United States court of a territory' within the jurisdiction of which the article is found. . . ."

Act § 505(a); 21 U.S.C. 355(a)

"(a) No person shall introduce or deliver for introduction into interstate commerce, any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug."

Act § 505(d); 21 U.S.C. 355(d)

"(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect

to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Act § 505(e); 21 U.S.C. 355(e)

"(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug, under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of

use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact. . . ."

Act § 505(h); 21 U.S.C. 355(h)

"(h) An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated

by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. . . ."

Judgment of Court of Appeals.

UNITED STATES COURT OF APPEALS

FOR THE THIRD CIRCUIT

No. 71-1512

CIBA CORPORATION,

Appellant,

vs.

ELLIOTT L. RICHARDSON, Secretary of Health, Education and Welfare and DR. CHARLES C. EDWARDS, Commissioner of Food and Drugs.

(D. C. Civil Action No. 1210-70)

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY

Present: HASTIE, VAN DUSEN and ALDISERT, *Circuit Judges.*

JUDGMENT

This cause came on to be heard on the record from the United States District Court for the District of New Jersey and was argued by counsel.

On consideration whereof, it is now here ordered and adjudged by this Court that the judgment of the said

District Court, filed March 10, 1971, be, and the same is hereby affirmed, with costs taxed against appellant.

ATTEST:

S/ THOMAS F. QUINN
Clerk

June 5, 1972
Certified as a true copy and issued in lieu of a formal mandate on June 27, 1972.

S/ THOMAS F. QUINN
Test: THOMAS F. QUINN
Clerk, United States Court of Appeals For The Third Circuit.

Opinion of Court of Appeals.

UNITED STATES COURT OF APPEALS
FOR THE THIRD CIRCUIT

No. 71-1512

CIBA CORPORATION, a corporation of the State of Delaware,
Appellant,

vs.

ELLIOTT L. RICHARDSON, Secretary of Health, Education & Welfare and DR. CHARLES C. EDWARDS, Commissioner of Food and Drugs.

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Argued April 11, 1972

Before: HASTIE, VAN DUSEN and ALDISERT, *Circuit Judges.*

OPINION OF THE COURT

[Filed June 5, 1972]

PER CURIAM:

Ciba Corporation has taken this appeal from an order of the District Court for the District of New Jersey dismissing a complaint in which Ciba sought a declaratory determination that its drug product, Ritonic Capsules, is exempt from the requirement of 1962 amendments of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355, that new drugs be excluded from the market unless proven effective as claimed for them. The complaint also sought an injunction against the implementation of an adminis-

trative order, entered by the Commissioner of Food and Drugs after notice and opportunity for an evidentiary hearing, that withdrew approval of the drug upon the basis of a finding that the manufacturer's claims as to its effectiveness were unproven. On appeal, the Court of Appeals for the Second Circuit has affirmed that order. *Ciba-Geigy Corp.* v. *Richardson*, 1971, 446 F.2d 466. That affirmance occurred after the district court had dismissed the present suit and is subject to review by the Supreme Court.

The appellant's basic position seems to be that neither the Commissioner in an administrative proceeding under § 355(e) to determine whether lack of effectiveness as claimed makes a drug unmarketable, nor a court of appeals in reviewing the administrative decision, has jurisdiction to decide as to threshold question whether the product in controversy is a "new drug" within the meaning of the statute, § 355, that covers "new drug" applications and administrative proceedings pursuant thereto. We find no merit in that argument. Inherent in the grant of administrative competency to conduct and decide new drug proceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such a proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision.

In disapproving Ritonic Capsules the Commissioner and the Court of Appeals for the Second Circuit necessarily decided that the 1962 amendments of the Act were applicable to that product. That determination is reviewable by the Supreme Court. It is neither necessary nor appropriate that the District Court for the District of New Jersey entertain a separate suit by the loser in the administrative proceeding and in the direct appeal therefrom for a redetermination of the same question.

The judgment will be affirmed.

Opinion of Court of Appeals for the Fourth Circuit in Bentex Pharmaceuticals, Inc. vs. Richardson.

UNITED STATES COURT OF APPEALS

FOR THE FOURTH CIRCUIT

No. 71-1243

BENTEX PHARMACEUTICALS, INC., et al.,

Appellants,

—versus—

ELLIOT L. RICHARDSON, Secretary of the Department of Health, Education and Welfare and CHARLES C. EDWARDS, Commissioner of the Food and Drug Administration,

Appellees.

Appeal from the United States District Court for the District of South Carolina, at Greenville. ROBERT W. HEMPHILL, District Judge.

(Argued December 8, 1971 Decided May 23, 1972.)

Before WINTER, RUSSELL and FIELD, Circuit Judges.

Opinion of Court of Appeals for the Fourth Circuit in Bentex Pharmaceuticals, Inc. vs. Richardson.

RUSSELL, Circuit Judge:

This appeal turns on a construction of the Federal Food, Drug and Cosmetic Act of 1938, as amended in 1962,[1] 21 U.S.C. 301, *et seq.* This statute requires pre-marketing approval and clearance of any "new drug" by the Secretary of Health, Education and Welfare.[2] The term "new drug" is defined as one "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof * * *."[3] From

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[1] There was an earlier Food and Drug Act of 1906. 34 Stat. 768 (1906). It did not provide for any pre-marketing review of the safety of drugs. The sulfanilamide episode in 1938 prompted the enactment of the Federal Food, Drug and Cosmetic Act of that year to replace the earlier Act and to provide, *inter alia*, for such pre-marketing review of "new drugs". See C. W. Dunn *Federal Food, Drug and Cosmetic Act—A Statement of Its Legislative Record*, pp. 1316-27 (1938). The fears generated by the thalidomide tragedies gave the impetus for the Amendments of 1962. See Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, 185 at p. 191, n. 45 (1971).

[2] Section 355(a), 21 U.S.C.

The actual approval of a "new drug" under the Act is normally processed by the Food and Drug Administration (FDA) in the Department of Health, Education and Welfare (HEW), and the approvals, when granted, are generally referred to as New Drug Approvals (NDAs). FDA, when used herein, refers to the Food and Drug Administration, and NDA is intended to describe an approval by FDA of a "new drug" application under the Act.

[3] Section 321 (p)(1), 21 U.S.C.

See, also, *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C.Md. 1967) 274 F. Supp. 443, 445, n. 2:

> "The statutory definition of the phrase 'new drug' controls this case, regardless of any other meaning attributable to the phrase or to the word 'new' by common understanding or other authority."

a denial of a pre-marketing approval or a withdrawal of a previously given approval, an appeal, originally to the District Court, now to the Circuit Court of Appeals, is authorized.[4] Drugs, which do not fit the definition of a "new drug" do not require FDA clearance for marketing. There is no provision in the Act for administrative determination whether a particular drug is a "new drug" nor for any right of appeal from any such determination. The FDA sometimes offers to render "informal advice" as to whether it considers a product a "new drug" but it uniformly designates such opinion "advice".[5] Accordingly, the responsibility for determining whether its product is a "new drug", requiring pre-marketing clearance by FDA, rests on the manufacturer, who must act at its peril.[6] If it makes an incorrect determination and seeks to market without FDA clearance a drug meeting the definition of a "new drug", it lays itself open to drastic judicial procedures that may be invoked by FDA, i.e.: The product may be seized in an *in rem* action instituted by the Government;[7] its sale may be enjoined in an action begun by the Government;[8] in addition, the manufacturer may be subjected to criminal action.[9] All these remedies must be prosecuted

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[4] Section 355(h), 21 U.S.C.

[5] 21 C.F.R. 130.39.

[6] Cf. *United States* v. *Dotterweich* (1943), 320 U. S. 277, 281, where, speaking of the Act of 1938, the Court said:

"In the interest of the larger good it puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger."

[7] Section 334, 21 U.S.C.

[8] Section 332, 21 U.S.C.

[9] Section 333, 21 U.S.C.

in the District Court and the role of the Secretary is that of plaintiff or prosecutor. The Act thus establishes two forums for the regulation of drugs: One is administrative and deals with the procedures for securing pre-marketing clearances for the statutorily defined "new drug", with right of appeal from a denial of approval, or withdrawal of a previous approval, to the District Court, later changed to the Court of Appeals; the other is judicial and is intended to make effective and give strength to the requirement that "new drugs" be cleared as safe before marketing by providing the Government with certain potent judicial remedies, *available exclusively in the District Court.*

Under the 1938 Act, a new drug was one "not generally recognized by experts * * * as safe for its intended use." The Amendments added "effectiveness" as well as "safety" to the definition. Simply stated, the change effected by the Amendments was that, whereas prior to the 1962 Amendments a drug which was generally recognized as safe was not a "new drug", the Amendments defined a drug as "new" if it were not generally recognized as both safe *and effective.* Furthermore, they replaced the provision for automatic approvals of applications not disapproved within a fixed time with a requirement of a positive act of approval on the part of FDA.[10] They proceeded to provide that the Secretary must find as a basis for clearance of a new drug not only safety but "substantial evidence" of effectiveness, "consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."

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[10] Section 355(c), 21 U.S.C.

The applicability of these amendments, including the revised definition of "new drug" to drugs already marketed, either under previously issued NDAs, or as "old drugs" requiring no FDA approval, was carefully spelt out in the Amendments and certain "grandfather rights" were granted. For all previously NDA'd drugs, the Amendments conferred a grace period of two years after the effective date of the Amendments within which to prepare evidence to satisfy the new requirement of efficacy added by the revised definition of "new drug"; during that "transitional" period no revocation or withdrawal of approval because of a lack of substantial evidence of efficacy of such drugs was permitted.[11] For a drug, however, which on the day prior to the enactment of the Amendments was (1) being "commercially used or sold in the United States," (2) "was not a new drug as defined by" the pre-Amendment statute and (3) "was not covered by an effective new drug application, * * *" "on the day immediately preceding the enactment date" of the Amendments, there was a permanent exemption from the efficacy provisions of the Amendments so long as the drug's labeling remained the same.[12] In summary, these provisions required that, "Those drugs which had obtained effective NDAs must be proven efficacious after two years; those

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[11] Section 107(c)(3), P.L. 87-781, Section 321, Supplement 1972, 21 U.S.C.

[12] Section 107(3)(4), P.L. 871-781, Section 321, 1972 Supplement, 21 U.S.C.; see, also, *Tyler Pharmacal Distrib. Inc.* v. *U.S. Dept.* v. *Health, E. & W.* (7th Cir. 1969), 408 F.2d 95, 99.

It should be noted that Section 321(p)(1) provides a "grandfather clause" applicable to pre-1938 drugs. This clause is not relevant to this action, which is concerned with drugs introduced between 1938 and 1962, and the subsequent references to "grandfather clause" in this opinion are to section 107(c)(4).

which had not need never be proven efficacious so long as they had become safe prior to the 1962 Amendments.'"[13]

The "grandfather clause" set forth in Section 107(c)(4) simply continues for the products satisfying its criteria the pre-1962 definition of a "new drug". Its effect is to assure that a drug which was generally recognized by qualified experts as safe for the purposes recommended for its use on October 9, 1962, need not be NDA'd as *effective* under the new requirements for the issuance of an NDA as a "new drug". But any drug, whether requiring an NDA or not, whether a "new drug" or an "old drug", is subject to the misbranding provisions of the Act and may be proceeded against on that basis. A false claim of either safety or effectiveness constitutes misbranding, rendering a drug subject to both civil and criminal penalties. *United States* v. *Article of Drug Labeled Decholin*

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[13] Note, *Drug efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, p. 196 (1971).

See, also, *United States* v. *Allan Drug Corp.* (10th Cir. 1966) 357 F. 2d 712, 719, note 9, quoting from the Supplemental Report of the Senate Committee on Drug Amendments of 1962, as set forth in the notes to Section 321, 21 U.S.C.:

> "Thirdly, in the case of a drug on the market which was never subject to the new-drug procedure before, the amendments to the new drug definition relating to drug effectiveness would not apply to existing labeling claims."

In the Conference Report of the House Managers on the Amendments, it was stated that the Amendments included "the Senate language providing with respect to existing label claims of drugs that have never previously been subject to the new-drug procedure substantially the same savings provisions as the corresponding provision of the House bill (Section 197(d))." *U. S. Code Congressional and Adminstrative News*, 87th Congress, 2d Session (1962), p. 2932. Again, in H.R. Rep. #2526, p. 23, it is stated that the exemption granted by the "grandfather clause" applies "to existing claims of drugs that have never been subject to the new-drug procedure".

(D.C. Mich. 1967), 264 F. Supp. 473, 482-3; *United States* v. *Lanpar Company* (D.C. Tex. 1968), 293 F. Supp. 147, 153-4.[14] Accordingly, in *United States* v. *Guardian Chemical Corporation* (2d Cir. 1969), 410 F. 2d 157, a drug manufacturer was acquitted of a charge of marketing a "new drug" without securing an NDA, but was convicted under a separate count of the indictment charging misbranding. "Thus", as one commentator has aptly stated, "the amplications of the FDA's authority (as granted by the 1962 Amendments) is (was) not due to the absence of power to proceed against ineffective drugs, but rather to authorize the exercise of that power at the initial stage, that is, *before* marketing, and also to shift the burden of proof to the applicant." Jurow, *The Effect on the Pharmaceutical Industry of the "Effectiveness" Provisions of the 1962 Drug Amendments,* 19 Food, Drug, Cosmetic Law Journal, 110, at p. 116 (1964).[15]

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[14] See, also, *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970), 434 F. 2d 536, 548:

"A good case could certainly be made that, quite apart from this, the 'efficacy' of a drug is necessarily related to the use recommended."

[15] See, also, Senate Report #1744, *U. S. Code Congressional and Administrative News,* 87th Cong., 2d Sess. (1962), pp. 2892 and 2893, where, in justifying the Amendments, it is stated:

"• • • where a drug is essentially innocuous, it (FDA) must clear the drug despite the fact that its claim of effectiveness is not borne out by the evidence. In such cases the Food and Drug Administration may proceed against the drug manufacturer by seizure of the drug for misbranding. However, the Department believes that the manufacturer should satisfy the Food and Drug Administration that his product is effective for the purposes claimed before it is marketed. • • • No question of safety is involved, and the Food and Drug Administration presently has ample power, including seizure, to proceed against any safe drug for which unsupported claims of effectiveness are made."

Opinion of Court of Appeals for the Fourth Circuit in Bentex Pharmaceuticals, Inc. vs. Richardson.

The plaintiffs, manufacturers of a prescription drug containing pentylenetetrazol and nicotinic acid, claim the protection of the "grandfather clause" included in Section 107(c)(4) for their products and that contention represents the substantive issue in this case. It is undisputed that plaintiffs had marketed their product commercially for many years prior to and on October 9, 1962,[16] without an NDA under the claim that it was not a "new drug" within the definition of the Act, and therefore required no NDA. Such claim was supported, it is asserted, both by previous informal advice of the Secretary and by the general recognition of the safety of such product by "experts qualified by scientific training and experience" to make such evaluation. The defendants, the Secretary of HEW and the Commissioner of Food and Drugs, in their brief, concede that "Over the years since 1938" and until 1968, the Food and Drug Administration had given the opinion that certain pentylenetetrazol combinations similar to those of the appellant were not "new drugs."[17] Moreover, the District Court observed in its opinion that there was "no contention (by the FDA) that the use of the plaintiffs' drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by

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[16] This was the day "immediately preceding the enactment date" of the Amendments of 1962.

[17] It is, of course, axiomatic that such opinions or advice can create no estoppel against the Government. *AMP Incorporated* v. *Gardner* (D.C.N.Y. 1967), 275 F. Supp. 410, 412, n. 1, aff. 389 F. 2d 825, cert. den. 393 U. S. 825, reh. den. 395 U. S. 917. The most that can be claimed for such opinions is that they lend color and good faith to the plaintiffs' claims. FDA not only has the right but is obligated to change its opinion if it learns its prior position was erroneous. *United States* v. *60 28—Capsule Bottles, More or Less, etc.* (D.C.N.J. 1962) 211 F. Supp. 207 , 215, aff. 325 F. 2d 513.

causing disuse of better drugs." On this basis, the plaintiffs contended that they met exactly the criteria established for exemption from the requirements of general recognition by qualified experts of the effectiveness of their products as provided in the permanent grandfather section of the 1962 Amendments.

Prior to the filing of this action, however, the defendants withdrew their advice that products such as those distributed by the plaintiffs were "old drugs" and contended that such products did not qualify for exemption under the "grandfather clause", Section 107(c)(4). The basis for this contention was the claim (1) that these drugs were not generally recognized by qualified experts as safe as of the effective date of the Amendments of 1962 and (2) that they were "me-too" drugs, whose marketability without FDA clearance depended in turn on the NDAs granted the basic drug, and for that reason must be regarded as drugs covered by an effective NDA on the effective date of the Amendments.[18] Faced with this threat, the plaintiffs began

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[18] The defendants assert that three "new drug" applications filed by other manufacturers and earlier approved by the FDA covered drugs similar in every particular to those marketed by the plaintiffs. Proceedings for withdrawal of the approval of such "new drugs" had been begun by FDA in advance of the filing of this action. In fact, such proceedings to a large extent prompted this action. It is the contention of the defendants that the withdrawal of what they describe as "the primary NDAs" operates to remove the marketability from what they assert are the "me-toos" or non-NDA'd drugs which are similar to other drugs which have secured effective NDAs. The plaintiffs deny that their drugs are like those previously NDA'd. They argue that those NDA'd products, unlike theirs, are intravenously administered or are a compound containing, in addition to the components of plaintiffs' drugs, reserpine. Such changes in formula or method of administering vitiated any claim by their manufacturers that they were marketing an old drug and required an approval as a new drug.

(*footnote continued on following page*)

this action for a declaratory judgment sustaining their right to exemption from proof of the effectiveness of their product and for injunctive relief awaiting the disposition of their claim for exemption. The defendants directed against the complaint a motion to dismiss or for summary judgment, which, in essence, (1) asserted primary jurisdiction in the Secretary to determine whether the products of the plaintiffs met the requirements for exemption under Section 107(c)(4), particularly whether they were "new drugs", requiring pre-marketing approval under the Act, (2) denied the propriety of a declaratory judgment action, and (3) claimed that the products of the plaintiffs were "new drugs" which did not qualify for exemption under the "grandfather clause".

The District Court sustained the right of the plaintiffs to maintain a suit for a declaratory judgment and the jurisdiction of the Court in such action to determine judicially whether the products of the plaintiffs were "new drugs", on the effective date of the Amendments, and whether they were or were not entitled to the benefits of

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(*footnote continued from preceding page*)

The plaintiffs assert their drugs are not subject to any such disability. These, however, are questions of fact not relevant to the simple questions of jurisdiction presented by this appeal and may be inquired into on remand. Even if the products of the plaintiffs be deemed "me-too" drugs (i.e., simply "a copy of a pioneer drug which preceded it on the market"), it is by no means clear that they do not "meet the requirements for section 107(c)(4) protection" and the argument of the Government to the contrary has been described as "lacking in merit." See, Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown Law Journal, 185 at pp. 203-207 (1971); *Hagan, Grandfather Protection under the Drug Amendments of 1962*, 19 Food Drug Cosmetic Law Journal, 119, at p. 125 (1964).

the "grandfather clause".[19] However,—and this is the nub of the controversy between the parties on this appeal—it concluded that the Secretary had concurrent jurisdiction to determine whether plaintiffs' products were "new drugs", requiring pre-marketing clearance, and that, because of the greater expertise of the Secretary in the field, it deferred to the Secretary's assumed jurisdiction to determine whether the drugs of the plaintiffs came within the exemption provided by the "grandfather clause". It enjoined any action against the plaintiffs and their products until the plaintiffs had been accorded a hearing before the Secretary on the issue of the qualifications of these drugs for protection under the "grandfather clause". It is the conclusion of concurrent jurisdiction in the Secretary and deference to that assumed concurrent jurisdiction from which the plaintiffs have prosecuted this appeal.

The defendants, on the other hand, have not cross-appealed and have accordingly acquiesced in the decision of the District Court that the action is properly maintainable as a declaratory judgment proceeding under Section 2201, 28 U.S.C. and that the District Court has jurisdiction over the substantive issue in this case, i.e., whether plain-

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[19] In support of the right of the plaintiffs to maintain a suit for declaratory judgment, the District Court relied on *Abbott Laboratories* v. *Gardner* (1967), 387 U. S. 136 and the companion case of *Toilet Goods Assn.* v. *Gardner* (1967), 387 U. S. 158. Additional support for such right is found in *AMP, Incorporated* v. *Gardner, supra; Durovic* v. *Richardson* (D.C. Ill. 1971), 327 F. Supp. 386; *Lemmon Pharmacal Co.* v. *Richardson* (D.C. Pa. 1970), 319 F. Supp. 375. The right of the Court to determine the applicability of the "grandfather clause" is equally clear and has been sustained in *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967), 274 F. Supp. 443, 445; and *United States* v. *Article Consisting of 36 Boxes, etc.* (D.C. Del. 1968), 284 F.Supp. 107, 112, n. 13, aff. 415 F.2d 369.

tiffs' products are "new drugs", as defined in the Act. The question in the case is thus whether the Secretary has concurrent jurisdiction to determine whether a drug is a "new drug" under the Act or whether that issue is cognizable only in the District Court. Contrary to the conclusion of the District Court, we conclude that the Act confers no such jurisdiction on the Secretary and, therefore, no basis for any deference by that Court to the concurrent jurisdiction of the Secretary.

The FDA has neither primary jurisdiction, as the defendants argue, nor concurrent jurisdiction, as the District Court concluded, to adjudicate whether a product is an old or a new drug. It may, in its prosecutorial role, reach a conclusion that a product being marketed is a "new drug" requiring pre-marketing approval; but that opinion is not adjudicatory, it is only the basis on which the FDA, as the prosecutor or iniator of either a seizure or injunctive action in the District Court, may invoke the jurisdiction of that Court to determine, among other issues, whether the drug challenged is a "new drug". There is manifestly no provision in the Act for an administrative proceeding before the Secretary to compel the filing of a "new drug" application or to halt the marketing of a drug for which there is no approval by the Secretary. It is not without significance that, so far as the official reports reflect, the Secretary has never attempted directly to exercise such jurisdiction. The only occasions on which he has sought to assert such jurisdiction has been as an element in his defense to a declaratory judgment action.[20] Moreover, when FDA undertook its new responsibilities under the

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[20] See, *Hynson, Westcott & Dunning, Inc.* v. *Richardson* (Civ. No. 21112, D. Md., decided 9/16/70); and *Ciba Corp.* v. *Richardson* (Civ. No. 1210-70, D. N.J., decided 3/10/71); but cf., *Lemmon Pharmacal, supra.*

1962 Amendments, it sought merely to review "the efficacy of *all new drugs that had been cleared,* for safety only, between 1938 and October 10, 1962" (Italics added) and enlisted the services of the National Academy of Sciences-National Research Council for this limited task. It did not assert the right to review, or assume the burden of reviewing, for efficacy, drugs such as those involved here, which had been commercially marketed on the basis of a general recognition of safety without an effective NDA as of the effective date of the 1962 Amendments. It, thus, recognized that its adjudicatory rights extended merely to the approval, or the withdrawal of approval,[22] of a drug embraced in a "new drug" application that had been approved. This confirms the conclusion that the halting of the marketing of a drug, for which there is no NDA, may not be by administrative action but must be by an injunction or *in rem* seizure proceeding, in which the Secretary appears, not in a judicial but in a prosecutorial role.[23] Those are the procedures prescribed and available to the Government under the Act.[24] The Secretary, it is true, has offered to provide

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[21] See *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970), 434 F.2d 536, 539, and 31 F.R. 9426.

[22] The authority of the Secretary to withdraw an approval of any "new drug" application filed under the Act of 1938 after hearing is specifically granted by Section 355(e), 21 U.S.C.

[23] Of course, in a proper case the Government may also institute criminal proceedings in the District Court. See Section 333, 21 U.S.C.

[24] Cf. *United States* v. *Allan Drug Corporation* (10th Cir. 1966), 357 F.2d 713, 718, cert. den. 385 U. S. 899, in which the Secretary is quoted to the effect that, "'As to drugs already on the market that have never been subject to the new-drug procedure but are not generally recognized as effective, the burden remains on the Government to prove *in court,* insofar as unchanged labeling claims are concerned, they do not have their claimed effect. If the labeling claims are changed, however, these must be approved under the new-drug procedure.'" (Italics added.)

"advice" on whether a product meets the qualification of an old drug but he categorizes his action in such instances as merely "advice" and makes no claim of finality therefor. Nor is there, as we have already observed, any provision for judicial review of such "advice".[25] The only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of an approval, of a "new drug" application.[26] That this is so follows from the limitations placed by the Act on judicial review of the decisions of the Secretary. The Secretary himself asserted, shortly after the enactment of the 1962 Amendments, in *Turkel* v. *Food and Drug Administration, Dept. of H.E.W., supra,* at p. 845, that the Act "grants a right to appeal only from an order of the Food and Drug Administration approving or disapproving a New Drug Application". In keeping with the Secretary's contention as to the extent of his adjudicatory powers, the Court in that case held that the right of appeal from an order of the Secretary "applies only to an order of the Secretary refusing or withdrawing approval of an application for sale and distribution of a new drug" (at pp. 845-6). It is not to be assumed that the Act confers an adjudicatory right on the Secretary from which no judicial review, however limited, is provided or allowed. Yet this is the unusual situation that would be presented if the Secretary were held to have jurisdiction to adjudicate whether a drug meets the statutory criteria of a "new drug".[27]

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[25] See *Turkel* v. *Food and Drug Administration, Dept. of H.E.W.* (6th Cir. 1964), 334 F.2d 844, 846, cert. denied 379 U. S. 990, rehearing denied 380 U.S. 927: "The jurisdiction of the United States Courts of Appeal to review administrative acts of federal agencies is wholly dependent upon statute."

[26] Section 355(b), 21 U.S.C.

[27] Cf., *Abbott Laboratories* v. *Gardner* (1967), 387 U. S. 136, at p. 140.

Opinion of Court of Appeals for the Fourth Circuit in Bentex Pharmaceuticals, Inc. vs. Richardson.

The District Court, in finding concurrent jurisdiction, held that "This grant of authority to approve or withhold approval of new drug application, * * * necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which required an approved new drug application for lawful interstate shipment." This reasoning assumes that an application for approval by the Secretary under the Act poses as its initial issue whether the product is a new drug. No such issue is posed by the application. The very filing of the application is a concession and recognition by the applicant-manufacturer that the article is a "new drug"; otherwise, there would be no reason to file the application. As a matter of fact, in the prescribed form of application, the applicant describes his product as "a new drug". 21 C.F.R. 130.4. The applicant makes the determination whether his product is a "new drug" and whether he must file for pre-marketing clearance by the Secretary. And when filed, the application puts in issue only one question: Is the article safe and effective? That and that alone is the issue to be considered by the Secretary in connection with an application for approval filed by a manufacturer under Section 355(d), 21 U.S.C. That issue is quite different from that presented when there is an issue whether a drug fits the statutory definition of "new drug" in the Act. The criterion for ascertaining whether a product is within the statutory definition of "new drug" under the Act is not safety and effectiveness *per se,* which, as we have observed, is the issue before the Secretary in connection with application for approval of a "new drug", but "whether the government has shown by a preponderance of the evidence that the 'drug' is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recom-

mended or suggested in the labeling thereof."[28] That is an issue that must be and is resolved, sometimes with, and at other times without a jury, in practically every injunctive, seizure, or criminal proceeding under the Act. See, for instance, *United States* v. *Articles of Drug Labeled "Quick-O-Ver", supra; United States* v. *41 Cases, More or Less* (5th Cir. 1970) 420 F.2d 1126, 1128; *United States* v. *Article of Drug, etc., supra,* at p. 392; *United States* v. *Article . . . Consist. of 216 Carton* (2d Cir. 1969), 409 F.2d 734, 742; *United States* v. *Article Consisting of 36 Boxes, etc., supra,* at p. 113; see, also, *United States* v. *Article of Drug, etc.* (D.C. Md. 1971), 331 F. Supp. 912, 915-7. That was one of the issues resolved in the declaratory action of *Lemmon Pharmacal Co.* v. *Richardson, supra.*[29] It is mani-

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[28] *United States* v. *Articles of Drug Labeled "Quick-O-Ver", supra,* at pp. 445-6.

See, also:

AMP, Incorporated v. *Gardner, supra,* at p. 831:

"But the safety of the products is not what is at issue here. The question is whether there is general recognition among qualified experts of the products' safety and effectiveness—if there is not, the products must be submitted to the Secretary of Health, Education and Welfare for a determination as to safety, adequacy of testing, etc."

United States v. *Article of Drug, etc.* (5th Cir. 1969), 415 F.2d 390, 392:

"Both sides agree that the nature of expert opinion about Furestrol, and not its actual safety or effectiveness, is the ultimate fact issue."

Cf. *United States* v. *Seven Cartons, More or Less, etc.* (7th Cir. 1970), 424 F.2d 1364, 1365.

[29] In discussing this case, the commentator in 60 Georgetown Law Journal, p. 199, note 87, says:

"In *Lemmon Pharmacal,* the Court, while noting that determining safety and efficacy would normally be within the primary jurisdiction of the agency, concluded that the question of section 107(c)(4) protection was properly before it."

festly a justiciable issue and the plaintiffs are entitled to a judgment on that issue by the Court, which alone has the jurisdiction to resolve it. In the absence of any statutory review proceedings within which they may assert their claim of exemption, the plaintiffs are not to be compelled to proceed at their peril, subject to the possibility of both civil and criminal penalties, but are entitled to seek relief by way of a declaratory judgment action. The District Court should accordingly have retained jurisdiction and proceeded to determine whether the plaintiffs' drugs met the criteria for exemption under Section 107 (c) (4). We deem it premature for us to consider at this stage, whether plaintiffs' products meet such criteria. That issue was not developed in the record before, or ruled on by, the District Court.[30] Upon remand, the issue can be considered by the Court in the light of the record that may be made by the parties.

REMANDED, WITH DIRECTIONS.

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[30] See *United States* v. *Article Consisting of 36 Boxes etc.*, *supra*, at p. 113.

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In the Supreme Court of the United States

OCTOBER TERM, 1972

No.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, PETITIONERS

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

The Solicitor General, on behalf of the Secretary of Health, Education, and Welfare and the Commissioner of Food and Drugs, petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Fourth Circuit in this case.

OPINIONS BELOW

The opinion of the court of appeals (App. A, *infra*, pp. 1a–17a) is not yet officially reported. The opinion of the district court (App. C, *infra*, pp. 19a–29a) is not reported.

JURISDICTION

The judgment of the court of appeals was entered on May 23, 1972 (App. B, *infra*, p. 18a). Mr. Justice Rehnquist extended the time within which to file a

petition for a writ of certiorari to October 5, 1972. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

QUESTION PRESENTED

Whether the Food and Drug Administration has jurisdiction to determine initially whether a product is a "new drug" which must be administratively approved as safe and effective before it can be sold in commerce.

STATUTES INVOLVED

Relevant provisions of the Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040, as amended by the Harris-Kefauver Act, 76 Stat. 780, 21 U.S.C. 301 *et seq.*, are set forth in Appendix D, *infra*, pp. 30a–32a.

The Administrative Procedure Act, 5 U.S.C. 551–559, 701–706, provides in pertinent part:

> § 554(e). The agency, with like effect as in the case of other orders, and in its sound discretion, may issue a declaratory order to terminate a controversy or remove uncertainty.
>
> § 703. The form of proceeding for judicial review is the special statutory review proceeding relevant to the subject matter in a court specified by statute or, in the absence or inadequacy thereof, any applicable form of legal action, including actions for declaratory judgments or writs of prohibitory or mandatory injunction or habeas corpus, in a court of competent jurisdiction. * * *
>
> § 704. Agency action made reviewable by statute and final agency action for which there is no other adequate remedy in a court are subject to judicial review. * * *

STATEMENT

This case, like *Richardson* v. *Hynson, Westcott and Dunning, Inc.*,[1] arises out of efforts by the Food and Drug Administration (FDA) to implement its congressionally imposed responsibility to insure that drugs on the market are effective for their intended uses.

In the Federal Food, Drug and Cosmetic Act of 1938, 52 Stat. 1040, Congress established a system of premarketing clearance for drugs. The Act prohibited the introduction of any "new drug" into interstate commerce unless an application approved by FDA was effective with respect to that drug (Section 505(a), 52 Stat. 1052). A "new drug" was defined as any drug not generally recognized by qualified experts as safe for its intended uses (Section 201(p)(1), 52 Stat. 1041–1042). The government could sue to enjoin violations of this prohibition, prosecute criminally, or proceed against the drugs in seizure and condemnation proceedings (Sections 301(d), 302(a), 303, 304, 52 Stat. 1042–1045). The Act established procedures for filing new drug applications (Section 505(b), 52 Stat. 1052) and provided standards under which, after notice and hearing, the agency could refuse to permit a new drug application (NDA) to become effective (Section 505(d), 52 Stat. 1052) or could suspend the effectiveness of an NDA (Section 505(e), 52 Stat. 1053). Such refusal and suspension orders could be reviewed in the district courts on the record made before the agency (Section 505(h), 52 Stat. 1053).

[1] Petition for a writ of certiorari filed Sept. 7, 1972, No. 72–354; cross-petition filed Sept. 11, 1972, No. 72–414.

In 1962, Congress adopted the Harris-Kefauver Amendments to the Act, which imposed new and broadened responsibilities on FDA and provided that, in order to be lawfully marketed, drugs must be *effective* for their intended uses as well as safe. The definition of "new drug" was revised to mean a drug not generally recognized by qualified experts as safe *and effective* for its intended uses (Section 201(p)(1), 21 U.S.C. 321(p)(1)). Congress expressly directed the agency to refuse approval for an NDA, and to withdraw prior approvals, if "substantial evidence" that the drug is effective for its intended uses is lacking (Sections 505(d) and (e), 21 U.S.C. 355(d) and (e)).[2] Thus, the basic clearance scheme requiring an administratively approved NDA before a "new drug" may be lawfully marketed was continued, as were the provisions for judicial enforcement of this requirement by injunction, seizure and criminal proceedings.[3]

To provide manufacturers an opportunity to develop substantial evidence of effectiveness, the amendments contained a grace period of two years during which previously approved NDAs could not be withdrawn by FDA for lack of effectiveness.[4] The amend-

[2] "Substantial evidence" was defined to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug" will be effective for its intended uses (Section 505(d), 21 U.S.C. 355(d)).

[3] Judicial review of refusals and withdrawals of approval for NDAs was transferred from the district courts to the courts of appeals (Section 505(h), 21 U.S.C. 355(h)).

[4] P.L. 87-781, Section 107(c)(3)(B), 76 Stat. 788-789, note following 21 U.S.C. 321 (1970 ed.).

ments also contained a "grandfather" clause exempting from the effectiveness requirement any drug which on the day preceding enactment (A) was commercially used or sold in the United States, (B) was not a "new drug" as defined in the 1938 Act (*i.e.*, was generally recognized as safe), and (C) "was not covered by an effective [new drug] application" under the 1938 Act.[5]

Of the 7,100 drugs for which approvals had been granted between 1938 and 1962, more than 4,000, involving approximately 16,700 claimed uses, were still on the market. In order to implement the congressional directive that ineffective drugs be removed from the market, FDA initiated a comprehensive efficacy review program—the "Drug Efficacy Study Implementation" (DESI). In 1966, FDA retained the National Academy of Sciences-National Research Council (NAS–NRC) to establish expert panels to review the efficacy claims of previously approved drugs. All holders of NDAs were invited to furnish the NAS–NRC panels the best data available to establish the effectiveness of their drugs (31 Fed. Reg. 9426). The panels then evaluated the material submitted to them and reported to the FDA, classifying the drugs as "effective," "probably effective," "possibly effective" and "ineffective." Drugs in any category other than "effective" are subject to withdrawal of approval.

In addition to the drugs for which NDAs had been issued, there were thousands of similar or identical formulations of other manufacturers that had come on the market without obtaining NDAs, in reliance

[5] P.L. 87–781, Section 107(c)(4), 76 Stat. 789, note following 21 U.S.C. 321 (1970 ed.).

upon the approval granted by FDA to the "pioneer" that they resembled. This case arises in the context of the FDA's efforts to remove these copies, called "me-too" drugs, from the market once the NDA for the ineffective "pioneer" has been withdrawn.

Proceedings before the FDA.—Under the pre–1962 standards, the agency had approved NDAs covering pentylenetetrazol combination drugs.[6] The NDAs were held by firms not involved in the present case. Three separate NAS–NRC panels reviewed the available evidence concerning the combinations (C.A. App., pp. E–R),[7] and each panel concluded that the drug was "ineffective" for each of its indicated uses (*id.* at pp. G, H, N, O, P, R).[8]

After evaluating the NAS–NRC reports on drug combinations containing pentylenetetrazol, the FDA concluded that there was a lack of substantial evidence that these drugs are effective for their intended uses. Accordingly, on August 26, 1969, it published a notice (34 Fed. Reg. 13673–13674) announcing its in-

[6] These are prescription drugs offered for senile psychosis and psychoneurosis, with anxiety and nervous tension, senile fatigue, confusion, debilitation, depression, dizzy spells, mild behavioral disorders, irritability and functional memory defects.

[7] "C.A. App." refers to the appendix to the appellees' brief in the court of appeals.

[8] The specific drugs evaluated were NICOZOL with RESERPINE (a combination of pentylenetetrazol, nicotinic acid and reserpine) which was evaluated by the panel on psychiatric drugs (C.A. App., pp. E–I) and GERONIAZOL injection (a combination of pentylenetetrazol and nicotinic acid administered by injection), which was evaluated by the panel on psychiatric drugs (*id.* at pp. N–O), the panel on drugs used in anesthesiology (*id.* at pp. P–Q), and the panel on drugs used in respiratory disturbances (*id.* at p. R).

tention to initiate proceedings to withdraw approval of the NDAs for these drugs. The notice invited the holders of NDAs "and any interested person who might be adversely affected by [the drugs'] removal from the market" to submit, within 30 days, any "adequate and well-controlled studies bearing on the efficacy of" the drugs in question. It also stated that promulgation of an order withdrawing approval of the NDAs would cause any drug containing the same substances to be a "new drug" for which an approved NDA is not in effect, and hence subject to "regulatory action."

Only one firm submitted further material in response. On May 20, 1970, the FDA announced that substantial evidence of effectiveness was lacking and that the prior approvals were to be withdrawn. The three firms which held approved NDAs and "any other interested person who may be adversely affected by such action" were offered an opportunity for a hearing. The agency also again declared that withdrawal of approval for the NDAs would cause any drug containing the same substances to be a "new drug" for which an approved NDA is not in effect. 35 Fed. Reg. 7749. Only one NDA holder requested a hearing, but it filed no material to support its request. The Commissioner therefore withdrew approval for the three NDAs then in effect. 35 Fed. Reg. 14412. No appeal was taken to review this action.

After its decision on the pentylenetetrazol NDAs, the agency took steps to remove from the market all "me-too" drugs containing that product. For example, on November 4, 1970, FDA wrote Bentex Pharma-

ceuticals advising it of FDA's action withdrawing approval for NDAs on drugs similar to Bentex products containing pentylenetetrazol and stating that, in view of this, those Bentex products were no longer marketable (App. C, *infra*, p. 24a, n. 3).

Decision of the District Court.—On December 1, 1970, Bentex and 23 other firms that market drugs containing pentylenetetrazol filed this suit for declaratory and injunctive relief. They contended that their drugs containing pentylenetetrazol either are not "new drugs" within the meaning of the amended Act or are exempt from the requirements of the amended Act by virtue of the grandfather clause. They accordingly sought a ruling declaring invalid and unenforceable the Commissioner's position that their drugs are "new drugs" for which no NDA is in effect and which therefore cannot legally be marketed.

The district court held that it had concurrent jurisdiction with the agency to determine whether plaintiffs' drugs are subject to the premarketing clearance procedure of the amended Act (App. C, *infra*, pp. 19a–29a). In so doing, it rejected both the government's contention that FDA has primary and exclusive jurisdiction to determine that issue (*id.* at 26a) and the manufacturers' contention that the question whether their drugs are "new drugs" requiring approved NDAs can be decided only by the district court (*id.* at 25a). The court ruled that the statutory "grant of authority to approve or withhold approval of new drug application [*sic*], or to proceed with regulatory action in the courts [by seizure, criminal prosecution or injunctive proceedings], necessarily implies

authority for F.D.A. to determine the threshold question of whether the article involved is a drug which requires an approved new drug application for lawful interstate shipment" (*ibid.*).

Having found concurrent jurisdiction, the district court concluded that the FDA, as "the more able arbiter of the question," should resolve the "new drug" issue at an administrative hearing in which plaintiffs and any other interested persons could participate (*id.* at 27a).[9] The court entered an injunction to preserve the *status quo,* barring enforcement proceedings against the drugs in question pending resolution of the "new drug" issue by FDA. If the agency declined to hold a hearing, the court said it would then determine the issue (*id.* at 29a).

Decision of the Court of Appeals.—On appeal by the plaintiff drug manufacturers,[10] the court of appeals reversed and remanded the case to the district court for it to determine whether plaintiffs' drugs are "new drugs" within the meaning of the Act (App. A, *infra,* pp. 1a–17a). The court of appeals held that the Act confers no jurisdiction on FDA, either primary or concurrent, to adjudicate administratively the question whether a drug is a "new drug" within the meaning of the Act, and that there is thus no basis for referring that question to the agency (*id.* at 12a). The court of appeals reached this conclu-

[9] The district court stated that an appeal from the FDA's determination would lie to the court of appeals (*id.* at 27a). We believe that the FDA's determination in response to the district court's referral order would be reviewable in the district court. See text accompanying note 16, *infra.*

[10] The government did not appeal.

sion because the plaintiffs were not holders of NDAs for these drugs and, under its view of the statutory scheme, "[t]he only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of an approval, of a 'new drug' application" (*id.* at 14a). In the court's view, it is only in the prosecutorial context that FDA is authorized to challenge the status of a drug, and in that context the question whether a product is a "new drug" is exclusively for the courts to decide (*id.* at 12a–13a).

The court of appeals pointed out that the Act does not expressly provide for judicial review of an administrative adjudication of the status of a drug, except in the context of refusal or withdrawal of an NDA. It reasoned that the Act therefore does not confer administrative power to make such an adjudication where no NDA is outstanding and none is sought by the manufacturer (*id.* at 14a–15a).

The court of appeals also rejected the district court's reasoning that the agency has inherent authority to resolve the threshold question of its jurisdiction. No question of whether an article is a "new drug" is presented by the filing of an application, in the court of appeals' view, because the act of applying for approval represents a concession by the manufacturer that the article is a "new drug" (*id.* at 15a). The court held that if the manufacturer chooses not to make that concession, but rather to proceed with marketing at its peril, the courts provide the only forum in which the legality of its actions may be adjudicated.

Since no record had been made in the district court on the issue whether the plaintiffs' drugs are "new

drugs," the case was remanded for determination of that question.

REASONS FOR GRANTING THE WRIT

The court of appeals' holding that FDA lacks power to determine whether particular drugs require an approved NDA to be lawfully marketed raises an important issue concerning the relationship of the courts and the agency in the administration of the Federal Food, Drug, and Cosmetic Act. It upsets the statutory scheme for administrative pre-market clearance by making the federal courts the exclusive forum for determining, *de novo,* the question on which the agency's jurisdiction turns—whether a product is a "new drug." By inviting transfer to the courts of an enormous volume of litigation concerning this threshold question, the holding below threatens to impair seriously the agency's efforts to remove ineffective drugs from the market. Moreover, the decision conflicts with a recent decision by the Third Circuit (*Ciba Corporation* v. *Richardson,* No. 71–1512, decided June 5, 1972, petition for a writ of certiorari filed October 2, 1972, No. 72–528.

Under Section 505(a) of the Act, a "new drug" may not be sold in interstate commerce unless an NDA for it has been approved by the Food and Drug Administration. A product that is not a "new drug," on the other hand, may be sold freely if not adulterated or misbranded. The agency's jurisdiction, therefore, depends initially on whether a product is a "new drug" within the meaning of the statute. The court below held, however, that the agency is without power to

make this threshold determination and that only the courts may do so. This decision goes to the heart of the scheme for premarketing clearance contemplated by the Act. For, if the agency cannot definitively determine whether a product is a new drug, drug manufacturers cannot look to it to learn with assurance whether their product requires agency approval in order to be marketed. They must either sell the drug in commerce at their own (and the public's) peril, or seek a judicial resolution of the agency's jurisdiction in a declaratory judgment action. Indeed, even if the manufacturer "concedes" that his product is a new drug by filing an application for agency approval, the FDA, under the court of appeals' view, could not determine the jurisdictional question. If the agency denies the application or thereafter withdraws approval, the court of appeals on review would either have to determine the "new drug" question *de novo* or render a decision that, for all practical purposes, is subject to relitigation in a declaratory judgment action.

The decision below would thus effectively transfer to the courts in all instances the determination of the complex medical and pharmacological questions upon which the definition of "new drug" turns. Nothing in the Act requires this unhappy result. On the contrary, Congress assigned to the agency a responsibility affecting the lives and health of millions—to determine in advance of marketing whether drugs are safe and effective. This responsibility carries with it the grant of express and implicit powers necessary for the

achievement of the Act's ultimate purposes.[11] Prominent among these is the power to decide the threshold questions on which the agency's jurisdiction turns.[12]

The Third Circuit's recent decision in *Ciba Corporation* v. *Richardson, supra,* reflects these principles. In that case, the agency withdrew an NDA held by Ciba for Ritonic Capsules. Ciba attacked the withdrawal in two separate judicial proceedings. It petitioned for review of the withdrawal order in the Second Circuit pursuant to Section 505(h) (21 U.S.C. 355(h)), and it filed a declaratory judgment action in a federal district court in New Jersey, claiming that its product was not a "new drug" and therefore was exempt from the Act's requirements. The district court dismissed Ciba's complaint, while the Court of Appeals for the Second Circuit affirmed the agency's withdrawal order. *Ciba-Geigy Corp.* v *Richardson,* 446 F.2d 466. On appeal from the dismissal of its district court action, Ciba contended to the Court of Appeals for the Third Circuit that neither the FDA nor the court of appeals on review of the agency's action had jurisdiction to determine whether Ritonic Capsules are a "new drug" subject to the Act, and that it was entitled to litigate this issue in full in the district court. The court held, however, that the agency necessarily is empowered to decide the threshold question as an incident of its power to approve or withdraw approval of NDAs and that its decision on that issue is review-

[11] See *Permian Basin Area Rate Cases,* 390 U.S. 747, 780; *United States* v. *Southwestern Cable Co.,* 392 U.S. 157, 177–178; *United States* v. *Midwest Video Corp.,* 406 U.S. 649.

[12] Cf. *Oklahoma Press Publishing Co.* v. *Walling,* 327 U.S. 186, 210–211.

able in the courts of appeals on direct appeal from the agency's order:

> Inherent in the grant of administrative competency to conduct and decide new drug proceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision.
>
> In disapproving Ritonic Capsules the Commissioner and the Court of Appeals for the Second Circuit necessarily decided that the 1962 amendments of the Act were applicable to that product. * * *

2. The facts of the instant case illustrate the potentially debilitating impact of the decision below on FDA's efforts to discharge its congressionally assigned responsibility to remove ineffective drugs from the market. Following an NAS–NRC finding of ineffectiveness, the agency here made an administrative determination that there is no substantial evidence that drugs containing pentylenetetrazol are effective and withdrew NDAs that had been approved prior to 1962, when safety was the sole criterion. This determination was not appealed and thus became final. However, the action directly affected only the three NDAs that were outstanding for products featuring this drug. Many other manufacturers had products on the market that appeared, in FDA's view, to be mere copies of the drugs found ineffective. Since these "me-too" drugs had never been through the NDA process, although they had apparently come on the market in reliance upon the pioneers' NDAs,

there was no physical piece of paper for FDA to withdraw. Clearly, in FDA's view, if these were in fact the same drugs and were as ineffective as the pioneers, Congress wanted them removed from the market too. The question posed by this case is whether meaningful administrative action toward this end can be taken, or whether all the complex questions involved in the "me-too" area must be resolved exclusively by the courts.

After withdrawal of the pioneers' NDAs, the types of questions raised regarding the status of "me-toos" as new drugs (requiring an approved NDA to remain on the market) can be highly technical and are not well suited for initial determination by the judiciary. For example, a manufacturer may assert that its drug is now generally recognized as safe and effective and is therefore not a "new drug" within the meaning of Section 201(p)(1) of the Act. Although this would be a difficult proposition to establish where the "me-too" drug is identical to the pioneer drug, in light of FDA's finding that substantial evidence of the pioneer drug's effectiveness is lacking, the "me-too" manufacturers may claim, as they did here, that their drugs are significantly different from the pioneers, and that the general recognition of their safety and effectiveness must be separately assessed. The "me-too" manufacturer may also claim exemption from the effectiveness requirement of the Act by virtue of the "grandfather" protection of Section 107(c)(4). Resolution of the grandfather claim would, in the normal case, involve ruling on whether the "me-too" drug was "covered" by the approved NDA of the pioneer

drug in October 1962 (Section 107(c)(4)(C)), and, if not, whether the "me-too" drug in question was generally recognized as safe at that time (Section 107(c)(4)(B)).[13]

These are the kinds of questions the court below ruled FDA has no jurisdiction to determine. This ruling would transfer to the district courts an enormous volume of litigation, necessitating trials on complex medical and chemical issues, with the result that resolution of the "new drug" status of the numerous "me-too" drugs currently on the market would be substantially delayed.[14]

---

[13] It is the position of FDA that a drug that is found to be a "me-too" would have been "covered" by an effective NDA at the time of the 1962 amendments and would therefore not be within the grandfather provision of Section 107(c)(4). The manufacturers contend that only NDA holders themselves are "covered" and that all "me-toos" are eligible for grandfather protection. Since neither the district court nor the court of appeals ruled on the merits of these contentions, the substantive issue whether plaintiffs' drugs are subject to the Act's effectiveness requirements is not directly involved in this petition. On remand, however, the issue would apparently be controlled by a decision of the same panel of the Fourth Circuit in *USV Pharmaceutical Corp.* v. *Richardson*, 461 F. 2d 223. In *USV*, the court held that "me-too" drugs produced by the same manufacturer who holds the pioneer NDA are "covered" and thus not "grandfathered," but made clear in its opinion that, contrary to FDA's contention, other manufacturers of "me-toos" would not be considered "covered." USV has been granted an extension of time within which to petition for a writ of certiorari.

[14] The NAS–NRC reports have led to the initial conclusion that approximately 1,350 drugs (involving more than 12,000 claimed uses), having NDAs approved between 1938 and 1962, fall within categories other than "effective" and are subject to possible withdrawal from the market. For each of these, it is estimated that there are, on the average, thirteen "me-too"

3. It is, we believe, both unwise and unnecessary for this obligation of initially determining the applicability of the Act to be imposed on district judges, whose dockets are already overcrowded and who generally do not have a background in medicine or chemistry.

Under the Act, the agency is assigned the primary role of determining whether, under statutory standards, new drugs ought to be made available to the public. The courts are assigned the important but secondary role of serving as the tribunal in which the agency can seek sanctions for non-compliance with the Act. The denial of agency power to determine the coverage of the Act it administers would reverse those roles, and the courts rather than the agency would become the primary tribunal for determining whether resort to the premarketing clearance procedures before the agency is necessary.

It is true that the agency cannot itself require a drug manufacturer to remove its product from the market. Contrary to the conclusion of the court below, however, we believe that the agency can provide an administrative remedy to determine whether "me-toos" are new drugs even though no procedure is

copies on the market for which no NDA was ever approved. In the present case, indeed, there are 23 plaintiffs, each of whom presumably manufactures a pentylenetetrazol product for which no NDA was ever issued, and each of whom presumably would have a right to bring a separate declaratory judgment proceeding. Neither the FDA nor the courts have the resources to deal effectively with this problem if it must be handled exclusively by the judiciary on a case-by-case basis.

specifically prescribed in the Act.[15] For the Administrative Procedure Act expressly enables FDA, like any other administrative agency, to issue "a declaratory order to terminate a controversy or remove uncertainty" (5 U.S.C. 554(e)). Such a declaratory order is subject to judicial review either in the district courts or the courts of appeals, depending upon the context in which it might be entered.

Thus, if the agency's declaratory order as to the status of a particular drug is unaccompanied by an order denying or withdrawing approval of an NDA, the order would be reviewable in the district courts,[16] since the Federal Food, Drug, and Cosmetic Act limits direct court of appeals review to orders denying or withdrawing approval of an NDA (Section 505(h), 21 U.S.C. 355(h)). If, however, the agency's determi-

[15] It is arguable that in circumstances involving technical questions in which agencies have special expertise, the courts should be required to defer to the agencies under the primary jurisdiction doctrine. See, *e.g.*, *United States* v. *Western Pacific R. Co.*, 352 U.S. 59, 62–70. In the present case, the government argued in the district court that FDA had primary jurisdiction and that the declaratory judgment action should be dismissed. Cf. *Far East Conference* v. *United States*, 342 U.S. 570, 576–577. But after the district court had ruled that it had concurrent jurisdiction, thereby rejecting the primary jurisdiction contention, it nevertheless referred the "new drug" question to the agency in the exercise of its equitable discretion. The government acquiesced in this determination and did not raise the primary jurisdiction argument on appeal. Consequently it is not presented in this petition. The agency believes, however, that where its regulations provide a uniform procedure for determination of issues within its responsibility, it has primary jurisdiction, and it will continue to assert this position where appropriate.

[16] Cf. *Citizens to Preserve Overton Park* v. *Volpe*, 401 U.S. 402.

nation of the "new drug" issue is made in a proceeding which results in the denial or withdrawal of an NDA, it would be reviewable, along with the denial or withdrawal order, in a court of appeals pursuant to Section 505(h).[17]

As the *Ciba Corporation* decision recognized, the power of the agency to determine administratively whether the Act's premarketing clearance procedure is applicable to particular drugs follows by necessary implication from the terms of the Act and the responsibilities it imposes.

For these reasons, we believe that the district court in the present case properly referred to the agency the question whether plaintiffs' drugs are subject to the Act's premarketing clearance procedure. The declaratory judgment remedy is discretionary. *Abbott Laboratories* v. *Gardner,* 387 U.S. 136, 148. The district court's decision to withhold that remedy until the agency, with the benefit of its expertise, had made a determination of the complex legal and factual issues involved was a permissible and appropriate exercise of its equitable discretion.

The court of appeals' reliance (App. A, *infra,* pp. 15a–16a) on the difference between the question involved in an agency proceeding for the approval or withdrawal of an NDA (safety and effectiveness in fact) and in a judicial enforcement proceeding (general recognition of safety and effectiveness) does not support the court's conclusion that the agency may never determine the latter issue in an administrative proceeding. The agency is at least as compe-

[17] *Ciba Corporation* v. *Richardson, supra.*

tent to decide that issue initially as are the district courts, if not more so. Indeed, the district court here frankly acknowledged that the agency is the "more able arbiter" of that question (App. C, *infra*, p. 27a).

Nor is the power of the courts to determine in an enforcement proceeding whether a particular drug is subject to the Act's premarketing clearance requirements a ground for concluding that the agency may never initially decide that question. Enforcement proceedings are the last resort under the statutory scheme; the threat of these enforcement proceedings, including criminal prosecution, is designed to channel manufacturers to the agency for premarketing clearance in the first instance.

There is, in short, no persuasive legal justification for the holding below that FDA has no authority to decide the threshold question whether the Act's premarketing clearance procedure applies to particular drugs. Unless overturned, that holding will impede substantially the agency's efforts to remove from the market drugs whose effectiveness cannot be shown. Achievement of one of the principal goals of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act—ensuring that drugs available to consumers are both safe and effective—thus would, at a minimum, be seriously delayed.[18]

[18] Only recently, FDA was criticized by a district judge for lack of expedition in carrying out this program. *American Public Health Ass'n.* v. *Veneman*, D.D.C., Civ. Action No. 1847-70, decided August 23, 1972 (holding that FDA must release to the public the NAS-NRC effectiveness reports it has not yet made public).

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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OCTOBER 1972.

APPENDIX A

United States Court of Appeals for the Fourth Circuit

No. 71-1243

BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMACEUTICAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC., SOUTHERN DRUG & MFG. CO., THE BLAINE COMPANY, BROWN PHARMACEUTICAL CO., MAYRAND, INC., PHARMACEUTICAL ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHARMACEUTICALS, INC., BCR PHARMACAL CO., INC., ALTO PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES, INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMACEUTICAL PRODUCTS, INC., FOS PHARMACEUTICAL CO., W. E. BOODY & CO., APPELLANTS

v.

ELLIOT P. RICHARDSON, SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, APPELLEES

Appeal From the United States District Court for the District of South Carolina, at Greenville. Robert W. Hemphill, District Judge

Argued December 8, 1971—Decided May 23, 1972

Before WINTER, RUSSELL, and FIELD, Circuit Judges

George F. Townes (*Sol E. Abrams* on brief) for Appellants, and *Charles R. McConachie,* Attorney,

477-696—72——4

Department of Justice (*Will Wilson*, Assistant Attorney General, *John L. Murphy*, Chief, Administrative Regulations Section, *William W. Goodrich*, Assistant General Counsel, Food, Drugs, and Environmental Health Division, *Robert N. Anderson*, Attorney, United States Department of Health, Education, and Welfare, and *Howard S. Epstein*, Attorney, Department of Justice, on brief) for Appellees.

RUSSELL, *Circuit Judge:* This appeal turns on a construction of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1962.[1] 21 U.S.C. 301, *et seq.* This statute requires pre-marketing approval and clearance of any "new drug" by the Secretary of Health, Education, and Welfare.[2] The term "new drug" is defined as one "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condi-

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[1] There was an earlier Food and Drug Act of 1906. 34 Stat. 768 (1906). It did not provide for any pre-marketing review of the safety of drugs. The sulfanilamide episode in 1938 prompted the enactment of the Federal Food, Drug and Cosmetic Act of that year to replace the earlier Act and to provide, *inter alia*, for such pre-marketing review of "new drugs". See C. W. Dunn, *Federal Food, Drug and Cosmetic Act—A Statement of Its Legislative Record*, pp. 1316–27 (1938). The fears generated by the thalidomide tragedies gave the impetus for the Amendments of 1962. See Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, 185 at p. 191, n. 45 (1971).

[2] Section 355(a), 21 U.S.C.

The actual approval of a "new drug" under the Act is normally processed by the Food and Drug Administration (FDA) in the Department of Health, Education and Welfare (HEW), and the approvals, when granted, are generally referred to as New Drug Approvals (NDAs). FDA, when used herein, refers to the Food and Drug Administration, and NDA is intended to describe an approval by FDA of a "new drug" application under the Act.

tions prescribed, recommended, or suggested in the labeling thereof * * *."[3] From a denial of a pre-marketing approval or a withdrawal of a previously given approval, an appeal, originally to the District Court, now to the Circuit Court of Appeals, is authorized.[4] Drugs, which do not fit the definition of a "new drug"[5] do not require FDA clearance for marketing. There is no provision in the Act for administrative determination whether a particular drug is a "new drug" nor for any right of appeal from any such determination. The FDA sometimes offers to render "informal advice" as to whether it considers a product a "new drug" but it uniformly designates such opinion "advice".[6] Accordingly, the responsibility for determining whether its product is a "new drug", requiring pre-marketing clearance by FDA, rests on the manufacturer, who must act at its peril.[7] If it makes an incorrect determination and seeks to market without FDA clearance a drug meeting the definition of a "new drug", it lays itself open to drastic judicial procedures that may be invoked by FDA, i.e.: The product may be seized in an *in rem* action instituted by the Government;[8] its sale may be enjoined in an action

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[3] Section 321(p)(1), 21 U.S.C.

See, also, *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F. Supp. 443, 445, n. 2:

"The statutory definition of the phrase 'new drug' controls this case, regardless of any other meaning attributable to the phrase or to the word 'new' by common understanding or other authority."

[4] Section 355(h), 21 U.S.C.

[5] 21 C.F.R. 130.39.

[6] Cf. *United States* v. *Dotterweich* (1943) 320 U.S. 277, 281, where, speaking of the Act of 1938, the Court said:

"In the interest of the larger good it puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger."

[7] Section 334, 21 U.S.C.

begun by the Government;[8] in addition, the manufacturer may be subjected to criminal action.[9] All these remedies must be prosecuted in the District Court and the role of the Secretary is that of plaintiff or prosecutor. The Act thus establishes two forums for the regulation of drugs: One is administrative and deals with the procedures for securing pre-marketing clearances for the statutorily defined "new drug", with right of appeal from a denial of approval, or withdrawal of a previous approval, to the District Court, later changed to the Court of Appeals; the other is judicial and is intended to make effective and give strength to the requirement that "new drugs" be cleared as safe before marketing by providing the Government with certain potent judicial remedies, *available exclusively in the District Court.*

Under the 1938 Act, a new drug was one "not generally recognized by experts * * * as safe for its intended use." The Amendments added "effectiveness" as well as "safety" to the definition. Simply stated, the change effected by the Amendments was that, whereas prior to the 1962 Amendments a drug which was generally recognized as safe was not a "new drug", the Amendments defined a drug as "new" if it were not generally recognized as both safe *and effective.* Furthermore, they replaced the provision for automatic approvals of applications not disapproved within a fixed time with a requirement of a positive act of approval on the part of FDA.[10] They proceeded to provide that the Secretary must find as a basis for clearance of a new drug not only safety but "substantial evidence" of effectiveness, "consisting of adequate and well-controlled investigations, including clinical inves-

[8] Section 332, 21 U.S.C.
[9] Section 333, 21 U.S.C.
[10] Section 355(c), 21 U.S.C.

tigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." The applicability of these amendments, including the revised definition of "new drug" to drugs already marketed, either under previously issued NDAs, or as "old drugs" requiring no FDA approval, was carefully spelt out in the Amendments and certain "grandfather rights" were granted. For all previously NDA'd drugs, the Amendments conferred a grace period of two years after the effective date of the Amendments within which to prepare evidence to satisfy the new requirement of efficacy added by the revised definition of "new drug"; during that "transitional" period no revocation or withdrawal of approval because of a lack of substantial evidence of efficacy of such drugs was permitted.[11] For a drug, however, which on the day prior to the enactment of the Amendments was (1) being "commercially used or sold in the United States," (2) "was not a new drug as defined by" the pre-Amendment statute and (3) "was not covered by an effective (new drug application, * * *" "on the day immediately preceding the enactment date" of the Amendments, there was a permanent exemption from the efficacy provisions of the Amendments so long as the drug's labeling remained the same.[12] In summary, these provisions required

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[11] Section 107(c)(3), P.L. 87-781, Section 321, Supplement 1972, 21 U.S.C.

[12] Section 107(c)(4), P.L. 871-781, Section 321, 1972 Supplement, 21 U.S.C.; see, also, *Tyler Pharmacal Distrib. Inc.* v. *U.S. Dept. of Health, E. & W.* (7th Cir. 1969) 408 F. 2d 95, 99.

It should be noted that Section 321(p)(1) provides a "grandfather clause" applicable to pre-1938 drugs. This clause is not relevant to this action, which is concerned with drugs introduced between 1938 and 1962, and the subsequent references to "grandfather clause" in this opinion are to section 107(c)(4).

that, "Those drugs which had obtained effective NDAs must be proven efficacious after two years; those which had not need never be proven efficacious so long as they had become safe prior to the 1962 Amendments." [13]

The "grandfather clause" set forth in Section 107(c)(4) simply continues for the products satisfying its criteria the pre-1962 definition of a "new drug". Its effect is to assure that a drug which was generally recognized by qualified experts as safe for the purposes recommended for its use on October 9, 1962, need not be NDA'd as *effective* under the new requirements for the issuance of an NDA as a "new drug". But any drug, whether requiring an NDA or not, whether a "new drug" or an "old drug", is subject to the misbranding provisions of the Act and may be proceeded against on that basis. A false claim of

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[13] Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, p. 196 (1971).

See, also, *United States* v. *Allan Drug Corp.* (10th Cir. 1966) 357 F. 2d 712, 719, note 9, quoting from the Supplemental Report of the Senate Committee on Drug Amendments of 1962, as set forth in the notes to Section 321, 21 U.S.C.:

"Thirdly, in the case of a drug on the market which was never subject to the new-drug procedure before, the amendments to the new drug definition relating to drug effectiveness would not apply to existing labeling claims."

In the Conference Report of the House Managers on the Amendments, it was stated that the Amendments included "the Senate language providing with respect to existing label claims of drugs that have never previously been subject to the new-drug procedure substantially the same savings provisions as the corresponding provision of the House bill (Section 197(d))." *U.S. Code Congressional and Administrative News*, 87th Congress, 2d Session (1962), p. 2932. Again, in H.R. Rep. #2526, p. 23, it is stated that the exemption granted by the "grandfather clause" applies "to existing claims of drugs that have never been subject to the new-drug procedure".

either safety or effectiveness constitutes misbranding, rendering a drug subject to both civil and criminal penalties. *United States* v. *Article of Drug Labeled Decholin* (D.C. Mich. 1967) 264 F. Supp. 473, 482–3; *United States* v. *Lanpar Company* (D.C. Tex. 1968) 293 F. Supp. 147, 153–4.[14] Accordingly, in *United States* v. *Guardian Chemical Corporation* (2d Cir. 1969) 410 F. 2d 157, a drug manufacturer was acquitted of a charge of marketing a "new drug" without securing an NDA, but was convicted under a separate count of the indictment charging misbranding. "Thus", as one commentator has aptly stated, "the amplications of the FDA's authority (as granted by the 1962 Amendments) is (was) not due to the absence of power to proceed against ineffective drugs, but rather to authorize the exercise of that power at the initial stage, that is, *before* marketing, and also to shift the burden of proof to the applicant." Jurow, *The Effect on the Pharmaceutical Industry of the "Effectiveness" Provisions of the 1962 Drug Amendments,* 19 Food, Drug, Cosmetic Law Journal, 110, at p. 116 (1964).[15]

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[14] See, also, *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 548:

"A good case could certainly be made that, quite apart from this, the 'efficacy' of a drug is necessarily related to the use recommended."

[15] See, also, Senate Report #1744, *U.S. Code Congressional and Administrative News*, 87th Cong., 2d Sess. (1962), pp. 2892 and 2893, where, in justifying the Amendments, it is stated:

"* * * where a drug is essentially innocuous, it (FDA) must clear the drug despite the fact that its claim of effectiveness is not borne out by the evidence. In such cases the Food and Drug Administration may proceed against the drug manufacturer by seizure of the drug for misbranding. However, the Department believes that the manufacturer should satisfy the

The plaintiffs, manufacturers of a prescription drug containing pentylenetetrazol and nicotinic acid, claim the protection of the "grandfather clause" included in Section 107(c)(4) for their products and that contention represents the substantive issue in this case. It is undisputed that plaintiffs had marketed their product commercially for many years prior to and on October 9, 1962,[16] without an NDA under the claim that it was not a "new drug" within the definition of the Act, and therefore required no NDA. Such claim was supported, it is asserted, both by previous informal advice of the Secretary and by the general recognition of the safety of such product by "experts qualified by scientific training and experience" to make such evaluation. The defendants, the Secretary of HEW and the Commissioner of Food and Drugs, in their brief, concede that "Over the years since 1938" and until 1968, the Food and Drug Administration had given the opinion that certain pentylenetetrazol combinations similar to those of the appellant were not "new drugs."[17] Moreover, the District Court ob-

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Food and Drug Administration that his product is effective for the purposes claimed before it is marketed. * * * No question of safety is involved, and the Food and Drug Administration presently has ample power, including seizure, to proceed against any safe drug for which unsupported claims of effectiveness are made."

[16] This was the day "immediately preceding the enactment date" of the Amendments of 1962.

[17] It is, of course, axiomatic that such opinions or advice can create no estoppel against the Government. *AMP Incorporated* v. *Gardner* (D.C.N.Y. 1967) 275 F. Supp. 410, 412, n. 1, aff. 389 F. 2d 825, cert. den. 393 U.S. 825, reh. den. 395 U.S. 917. The most that can be claimed for such opinions is that they lend color and good faith to the plaintiffs' claims. FDA not only has the right but is obligated to change its opinion if it learns its prior position was erroneous. *United States* v. *60 28-Capsule Bottles, More or Less, etc.* (D.C.N.J. 1962) 211 F. Supp. 207, 215, aff. 325 F. 2d 513.

served in its opinion that there was "no contention (by the FDA) that the use of the plaintiffs' drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs." On this basis, the plaintiffs contended that they met exactly the criteria established for exemption from the requirements of general recognition by qualified experts of the effectiveness of their products as provided in the permanent grandfather section of the 1962 Amendments.

Prior to the filing of this action, however, the defendants withdrew their advice that products such as those distributed by the plaintiffs were "old drugs" and contended that such products did not qualify for exemption under the "grandfather clause", Section 107(c)(4). The basis for this contention was the claim (1) that these drugs were not generally recognized by qualified experts as safe as of the effective date of the Amendments of 1962 and (2) that they were "me-too" drugs, whose marketability without FDA clearance depended in turn on the NDAs granted the basic drug, and for that reason must be regarded as drugs covered by an effective NDA on the effective date of the Amendments.[18] Faced with this threat, the plaintiffs

[18] The defendants assert that three "new drug" applications filed by other manufacturers and earlier approved by the FDA covered drugs similar in every particular to those marketed by the plaintiffs. Proceedings for withdrawal of the approval of such "new drugs" had been begun by FDA in advance of the filing of this action. In fact, such proceedings to a large extent prompted this action. It is the contention of the defendants that the withdrawal of what they describe as "the primary NDAs" operates to remove the marketability from what they assert are the "me-toos" or non-NDA'd drugs which are similar to other drugs which have secured effective NDAs. The plaintiffs deny that their drugs are like those previously NDA'd.

began this action for a declaratory judgment sustaining their right to exemption from proof of the effectiveness of their product and for injunctive relief awaiting the disposition of their claim for exemption. The defendants directed against the complaint a motion to dismiss or for summary judgment, which, in essence, (1) asserted primary jurisdiction in the Secretary to determine whether the products of the plaintiffs met the requirements for exemption under Section 107(c)(4), particularly whether they were "new drugs", requiring pre-marketing approval under the Act, (2) denied the propriety of a declaratory judgment action, and (3) claimed that the products of the plaintiffs were "new drugs" which did not qualify for exemption under the "grandfather clause".

The District Court sustained the right of the plaintiffs to maintain a suit for a declaratory judgment and the jurisdiction of the Court in such action to determine judicially whether the products of the plaintiffs

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They argue that those NDA'd products, unlike theirs, are intravenously administered or are a compound containing, in addition to the components of plaintiffs' drugs, reserpine. Such changes in formula or method of administering vitiated any claim by their manufacturers that they were marketing an old drug and required an approval as a new drug. The plaintiffs assert their drugs are not subject to any such disability. These, however, are questions of fact not relevant to the simple question of jurisdiction presented by this appeal and may be inquired into on remand. Even if the products of the plaintiffs be deemed "me-too" drugs (i.e., simply "a copy of a pioneer drug which preceded it on the market"), it is by no means clear that they do not "meet the requirements for section 107(c)(4) protection" and the argument of the Government to the contrary has been described as "lacking in merit." See, Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown Law Journal, 185 at p. 203–207 (1971); Hagan, *Grandfather Protection under the Drug Amendments of 1962*, 19 Food Drug Cosmetic Law Journal, 119, at p. 125 (1964).

were "new drugs", on the effective date of the Amendments, and whether they were or were not entitled to the benefits of the "grandfather clause".[19] However—and this is the nub of the controversy between the parties on this appeal—it concluded that the Secretary had concurrent jurisdiction to determine whether plaintiffs' products were "new drugs", requiring premarketing clearance, and that, because of the greater expertise of the Secretary in the field, it deferred to the Secretary's assumed jurisdiction to determine whether the drugs of the plaintiffs came within the exemption provided by the "grandfather clause". It enjoined any action against the plaintiffs and their products until the plaintiffs had been accorded a hearing before the Secretary on the issue of the qualifications of these drugs for protection under the "grandfather clause". It is the conclusion of concurrent jurisdiction in the Secretary and deference to that assumed concurrent jurisdiction from which the plaintiffs have prosecuted this appeal.

The defendants, on the other hand, have not cross-appealed and have accordingly acquiesced in the decision of the District Court that the action is properly

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[19] In support of the right of the plaintiffs to maintain a suit for declaratory judgment, the District Court relied on *Abbott Laboratories* v. *Gardner* (1967) 387 U.S. 136 and the companion case of *Toilet Goods Assn.* v. *Gardner* (1967) 387 U.S. 158. Additional support for such right is found in *AMP, Incorporated* v. *Gardner, supra; Durovic* v. *Richardson* (D.C. Ill. 1971) 327 F. Supp. 386; *Lemmon Pharmacal Co.* v. *Richardson* (D.C. Pa. 1970) 319 F. Supp. 375. The right of the Court to determine the applicability of the "grandfather clause" is equally clear and has been sustained in *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F. Supp. 443, 445; and *United States* v. *Article Consisting of 36 Boxes, etc.* (D.C. Del. 1968) 284 F. Supp. 107, 112, n. 13, aff. 415 F. 2d 369.

maintainable as a declaratory judgment proceeding under Section 2201, 28 U.S.C. and that the District Court has jurisdiction over the substantive issue in this case, i.e., whether plaintiffs' products are "new drugs", as defined in the Act. The question in the case is thus whether the Secretary has concurrent jurisdiction to determine whether a drug is a "new drug" under the Act or whether that issue is cognizable only in the District Court. Contrary to the conclusion of the District Court, we conclude that the Act confers no such jurisdiction on the Secretary and, therefore, no basis for any deference by that Court to the concurrent jurisdiction of the Secretary.

The FDA has neither primary jurisdiction, as the defendants argue, nor concurrent jurisdiction, as the District Court concluded, to adjudicate whether a product is an old or a new drug. It may, in its prosecutorial role, reach a conclusion that a product being marketed is a "new drug" requiring pre-marketing approval; but that opinion is not adjudicatory, it is only the basis on which the FDA, as the prosecutor or initiator or either a seizure or injunctive action in the District Court, may invoke the jurisdiction of that Court to determine, among other issues, whether the drug challenged is a "new drug". There is manifestly no provision in the Act for an administrative proceeding before the Secretary to compel the filing of a "new drug" application or to halt the marketing of a drug for which there is no approval by the Secretary. It is not without significance that, so far as the official reports reflect, the Secretary has never attempted directly to exercise such jurisdiction. The only occasions on which he has sought to assert such jurisdiction has been as an element in his defense to a declaratory

judgment action.[20] Moreover, when FDA undertook its new responsibilities under 1962 Amendments, it sought merely to review "the efficacy of *all new drugs that had been cleared,* for safety only, between 1938 and October 10, 1962"[21] (Italics added) and enlisted the services of the National Academy of Sciences-National Research Council for this limited task. It did not assert the right to review, or assume the burden of reviewing, for efficacy, drugs such as those involved here, which had been commercially marketed on the basis of a general recognition of safety without an effective NDA as of the effective date of the 1962 Amendments. It, thus, recognized that its adjudicatory rights extended merely to the approval, or the withdrawal of approval,[22] of a drug embraced in a "new drug" application that had been approved. This confirms the conclusion that the halting of the marketing of a drug, for which there is no NDA, may not be by administrative action but must be by an injunction or *in rem* seizure proceeding, in which the Secretary appears, not in a judicial but in a prosecutorial role.[23] Those are the procedures prescribed and available to

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[20] See, *Hynson, Westcott & Dunning, Inc.* v. *Richardson* (Civ. No. 21112, D. Md., decided 9/16/70); and *Ciba Corp.* v. *Richardson* (Civ. No. 1210–70, D.N.J., decided 3/10/71); but cf., *Lemmon Pharmacal, supra.*

[21] See *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 539, and 31 F.R. 9426.

[22] The authority of the Secretary to withdraw an approval of any "new drug" application filed under the Act of 1938 after hearing is specifically granted by Section 355(e), 21 U.S.C.

[23] Of course, in a proper case the Government may also institute criminal proceedings in the District Court. See Section 333, 21 U.S.C.

the Government under the Act.[24] The Secretary, it is true, has offered to provide "advice" on whether a product meets the qualification of an old drug but he categorizes his action in such instances as merely "advice" and makes no claim of finality therefor. Nor is there, as we have already observed, any provision for judicial review of such "advice".[25] The only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of an approval, of a "new drug" application.[26] That this is so follows from the limitations placed by the Act on judicial review of the decisions of the Secretary. The Secretary himself asserted, shortly after the enactment of the 1962 Amendments, in *Turkel* v. *Food and Drug Administration, Dept. of H.E.W., supra,* at p. 845, that the Act "grants a right to appeal only from an order of the Food and Drug Administration approving or disapproving a New Drug Application". In keeping with the Secretary's contention as to the extent of his adjudicatory powers, the Court in that case held that the right of appeal from an order of the Secretary "applies only to an order of the Secretary refusing or

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[24] Cf. *United States* v. *Allan Drug Corporation* (10th Cir. 1966) 357 F. 2d 713, 718, cert. den. 385 U.S. 899, in which the Secretary is quoted to the effect that, " 'As to drugs already on the market that have never been subject to the new-drug procedure but are not generally recognized as effective, the burden remains on the Government to prove *in court*, insofar as unchanged labeling claims are concerned, they do not have their claimed effect. If the labeling claims are changed, however, these must be approved under the new-drug procedure.' " (Italics added.)

[25] See *Turkel* v. *Food and Drug Administration, Dept. of H.E.W.* (6th Cir. 1964) 334 F. 2d 844, 846, cert. denied 379 U.S. 990, rehearing denied 380 U.S. 927: "The jurisdiction of the United States Courts of Appeal to review administrative acts of federal agencies is wholly dependent upon statute."

[26] Section 355(b), 21 U.S.C.

withdrawing approval of an application for sale and distribution of a new drug" (at pp. 845–6). It is not to be assumed that the Act confers an adjudicatory right on the Secretary from which no judicial review, however limited, is provided or allowed. Yet this is the unusual situation that would be presented if the Secretary were held to have jurisdiction to adjudicate whether a drug meets the statutory criteria of a "new drug".[27]

The District Court, in finding concurrent jurisdiction, held that "This grant of authority to approve or withhold approval of new drug application, * * * necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which required an approved new drug application for lawful interstate shipment." This reasoning assumes that an application for approval by the Secretary under the Act poses as its initial issue whether the product is a new drug. No such issue is posed by the application. The very filing of the application is a concession and recognition by the applicant-manufacturer that the article is a "new drug"; otherwise, there would be no reason to file the application. As a matter of fact, in the prescribed form of application, the applicant describes his product as a "new drug". 21 C.F.R. 130.4. The applicant makes the determination whether his product is a "new drug" and whether he must file for pre-marketing clearance by the Secretary. And when filed, the application puts in issue only one question: Is the article safe and effective? That and that alone is the issue to be considered by the Secretary in connection with an application for approval filed by a manufacturer under Section 355(d), 21 U.S.C. That issue is quite different

[27] Cf., *Abbott Laboratories* v. *Gardner* (1967) 387 U.S. 136, at p. 140.

from that presented when there is an issue whether a drug fits the statutory definition of "new drug" in the Act. The criterion for ascertaining whether a product is within statutory definition of "new drug" under the Act is not safety and effectiveness *per se,* which, as we have observed, is the issue before the Secretary in connection with application for approval of a "new drug", but "whether the government has shown by a preponderance of the evidence that the drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof." [28] That is an issue that must be and is resolved, sometimes with, and at other times without a jury, in practically every injunctive, seizure, or criminal proceeding under the Act. See, for instance, *United States* v. *Articles of Drug Labeled "Quick-O-Ver", supra; United States* v. *41 Cases, More or Less* (5th Cir. 1970) 420 F. 2d 1126, 1128; *United States* v. *Article of Drug, etc., supra,* at p. 392;

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[28] *United States* v. *Articles of Drug Labeled "Quick-O-Ver", supra,* at pp. 445–6.

See, also: *AMP, Incorporated* v. *Gardner, supra,* at p. 831:

"But the safety of the products is not what is at issue here. The question is whether there is general recognition among qualified experts of the products' safety and effectiveness—if there is not, the products must be submitted to the Secretary of Health, Education, and Welfare for a determination as to safety, adequacy of testing, etc."

United States v. *Article of Drug, etc.* (5th Cir. 1969) 415 F. 2d 390, 392:

"Both sides agree that the nature of expert opinion about Furestrol, and not its actual safety or effectiveness, is the ultimate fact issue."

Cf., *United States* v. *Seven Cartons, More or Less, etc.* (7th Cir. 1970) 424 F. 2d 1364, 1365.

United States v. *Article . . . Consist. of 216 Carton* (2d Cir. 1969) 409 F. 2d 734, 742; *United States Article Consisting of 36 Boxes, etc., supra,* at p. 113; see, also, *United States* v. *Article of Drug, etc.* (D.C. Md. 1971) 331 F. Supp. 912, 915–7. That was one of the issues resolved in the declaratory action of *Lemmon Pharmacal Co.* v. *Richardson, supra.*[29] It is manifestly a justiciable issue and the plaintiffs are entitled to a judgment on that issue by the Court, which alone has the jurisdiction to resolve it. In the absence of any statutory review proceedings within which they may assert their claim of exemption, the plaintiffs are not to be compelled to proceed at their peril, subject to the possibility of both civil and criminal penalties, but are entitled to seek relief by way of a declaratory judgment action. The District Court should accordingly have retained jurisdiction and proceeded to determine whether the plaintiffs' drugs met the criteria for exemption under Section 107(c)(4). We deem it premature for us to consider at this stage whether plaintiffs' products meet such criteria. That issue was not developed in the record before, or ruled on by, the District Court.[30] Upon remand, the issue can be considered by the Court in the light of the record that may be made by the parties.

Remanded, with directions.

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[29] In discussing this case, the commentator in 60 Georgetown Law Journal, p. 199, note 87, says:

"In *Lemmon Pharmacal*, the Court, while noting that determining safety and efficacy would normally be within the primary jurisdiction of the agency, concluded that the question of section 107(c)(4) protection was properly before it."

[30] See *United States* v. *Article Consisting of 36 Boxes etc., supra,* at p. 113.

APPENDIX B

[Filed, May 23, 1972, Samuel W. Phillips, clerk.]

United States Court of Appeals for the Fourth Circuit

No. 71-1243

BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., ET AL., APPELLANTS

v.

ELLIOTT P. RICHARDSON, SECRETARY OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, APPELLEES

Judgment

Appeal from the United States District Court for the District of South Carolina.

This cause came on to be heard on the record from the United States District Court for the District of South Carolina, and was argued by counsel.

On consideration whereof, It is now here ordered and adjudged by this Court that the judgment of the said District Court appealed from, in this cause, be, and the same is hereby, reversed. The case is remanded to the United States District Court for the District of South Carolina, at Greenville, with directions consistent with the opinion of this Court filed herewith.

SAMUEL W. PHILLIPS,
Clerk.

APPENDIX C

[Original filed, February 10, 1971, Miller C. Foster, Jr., clerk]

In the District Court of the United States for the District of South Carolina, Greenville Division

Civil Action No. 70–1001

O'NEAL, JONES & FELDMAN, INC., BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMACEUTICAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC., SOUTHERN DRUG & MFG. CO., THE BLAINE COMPANY, BROWN PHARMACEUTICAL CO., MAYRAND, INC., PHARMACEUTICAL ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHARMACEUTICALS, INC., BCR PHARMACAL CO., INC., ALTO PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES, INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMACEUTICAL PRODUCTS, INC., FOS PHARMACEUTICAL CO., W. E. BOODY & CO., PLAINTIFFS

v.

ELLIOT P. RICHARDSON, SECRETARYY OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF THE FOOD AND DRUG ADMINISTRATION, DEFENDANTS

Order

This is a civil action for declaratory and injunctive relief brought by twenty-four pharmaceutical com-

panies aggrieved by the action of the Food and Drug Administration (hereinafter F.D.A.) respecting drugs containing pentylenetetrazol. The events leading to the commencement of this action may be summarized as follows: In August 1969 the F.D.A. announced in the FEDERAL REGISTER its intention to initiate proceedings to withdraw approval of new drug applications for two drugs containing pentylenetetrazol and nicotinic acid. (34 F.R. 13673) The drugs covered by those applications differed from those manufactured by the plaintiffs herein in that the product covered by one application was injected intravenously and the other application contained a third active ingredient, reserpine. The published notice invited the submission of data on the efficacy of the products by any interested person who might be adversely affected by the removal from the market of the drugs covered by the new drug applications. The notice further stated:

> Promulgation of the proposed order will cause any drug for human use containing the same active substances to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

None of the plaintiffs herein responded to the notice and in May 1970, a second notice was published stating that substantial evidence of the effectiveness of the drugs covered by the new drug applications had not been provided and that the approval of the applications would be withdrawn. Notice was also given that any affected person desirous of a hearing on the question should so elect within 30 days (35 F.R. 7749). That notice contained language concerning the effect on drugs other than those covered by the applications to be withdrawn substantially identical to the language of the August notice set out above.

In September 1970 the F.D.A. published its order withdrawing approval of the two new drug applications mentioned above and directing the recall of outstanding stocks of the drugs. 35 F.R. 14412.

Pursuant to its revocation of the two new drug applications, the F.D.A. took steps to effect the removal from the market of drugs containing pentylenetetrazol manufactured by various of the plaintiffs. By their complaint in this action the plaintiffs seek declaratory judgment determining the validity and enforceability of the order of the Secretary as it concerns their drugs and injunctive relief pendente lite. The defendant moves that the action be dismissed for want of jurisdiction and failure to state a claim for which relief can be granted.

The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, *et seq.*) effective in 1938, gave preclearance authority to the Food and Drug Administration to regulate the distribution of new drugs by a system of new-drug applications which had to be obtained before distribution of the drug in interstate channels was allowed. The early definition of new drugs, however, gave the Agency power to regulate these drugs and approve them on the basis of safety alone. The drug companies were not required to support their claims of effectiveness for the drug with appropriate medical data. Effective on October 10, 1962, the Act was amended to close this important gap in the regulatory power of the Agency. Under the provisions of the Act as amended, a drug not only must be proved safe, but also must be shown by "substantial evidence," to be effective for the indication and uses described in its labeling. The amendments also define "substantial evidence" as consisting of ". . . adequate and well-controlled investigations, including clinical investigations, by experts . . ." sufficient to

demonstrate that the drug works as claimed. [21 U.S.C. 355(d)]. The burden of producing evidence of effectiveness to support continued marketing of drugs which have already been cleared on the grounds of safety, is placed squarely on the drug manufacturers and distributors. [21 U.S.C. § 355(b)]. The Act as amended also gives the Secretary power to revoke approved new drug applications for several reasons among which is failure to submit substantial evidence of the effectiveness of the drug [21 U.S.C. 355(e)3]. It was pursuant to this authority that the Secretary issued the order by which the plaintiffs herein are aggrieved.

The Act grants the Secretary primary jurisdiction to make determinations regarding new drug applications and provides direct appeal from his orders to the circuit courts.[1]

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[1] 21 U.S.C. § 355(h). An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 23, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if sup-

The plaintiffs do not contend that this court has jurisdiction to consider the propriety of the Secretary's revocation of the two new drug applications. Rather they argue either that their drugs are not new drugs within the meaning of the Act or are within the grandfather clause;[2] and are therefore not subject to the Secretary's regulation of new drugs. The plaintiffs contend that seizure, injunction, or criminal prosecu-

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ported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the Court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

[2] 21 U.S.C. § 321(p). The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at

tion by the F.D.A. pursuant to 21 U.S.C. §§ 332–34 is imminent.[3] They urge that, rather than proceeding at their peril, they are entitled to declaratory relief adjudicating the merits of their respective contentions

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such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigation, been used to a material extent or for a material time under such conditions.

[3] The plaintiff Bentex Pharmaceutical Company received the following letter from the F.D.A.:

Nov. 4, 1970.

"This letter is written in reference to your products Benizol Tablets & Elizir, Benizol A-D Tablets, & Benizol Plus capsules & Elixir containing Pentylenetetrazol for human use.

"On September 12, 1970, an announcement published in the *Federal Register* setting forth the conclusion of the Food and Drug Administration that there is a lack of substantial evidence that drugs similar to yours are effective for the uses prescribed, recommended, or suggested in their labeling.

"Accordingly, the Commissioner of the Food and Drug Administration has withdrawn approval of the applicable new drug applications for such drugs.

"The withdrawal of all previously approved new drug applications causes any similar drug to be a new drug for which an approved new drug application is not in effect. Because these are no longer regarded as legal products, any such drug on the market is subject to regulatory proceedings under the applicable provisions of the Federal Food, Drug, and Cosmetic Act.

"We request your reply within 15 days after receipt of this letter stating your intentions with respect to removal of all outstanding stocks of your product to the retail level."

concerning the status of their drugs.[4] They argue persuasibly that they are entitled to a day in court on that question prior to the seizure of their products and possible criminal prosecution.

The plaintiffs urge that they can only have that day in this court. The court does not agree. The Act gives the F.D.A. authority to proceed by seizure action, criminal prosecution, or injunction, [21 U.S.C. 332–334] to clear the channels of interstate commerce of drugs which have improperly avoided the new drug procedures. This grant of authority to approve or withhold approval of new drug application, or to proceed with regulatory action in the courts, necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which requires an approved new drug application for lawful interstate shipment. The determination that a drug is a new drug is essential to any F.D.A. action regulating it by means of new drug applications. Therefore, the F.D.A. must have jurisdiction to make that determination.[5]

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[4] It appears that for a time drugs of the type in question were regarded as old drugs by the F.D.A. The record contains a letter dated Dec. 15, 1958 which reads in pertinent part as follows:

"As to your inquiry concerning the new drug status of a timed disintegration tablet containing Pentylenetetrazol 300 mg., Nicotinic Acid 150 mg.

"In our opinion this article is not a new drug as defined in section 201(p) of the Federal Food, Drug, and Cosmetic Act when distributed as a prescription preparation under the labeling which you have submitted." Statements such as the above were, however, revoked by the Secretary [21 C.F.R. 130.39].

[5] Hymson, Westcott and Dunning, Inc. v. Finch, C.A. 2112, D. Md., decided September 16, 1970, on facts represented to the court to be similar to the present case held that the F.D.A. could consider and decide questions determining the status of a drug and that review of that determination would be available pursuant to 21 U.S.C. 355(h) set out at n. 1, supra.

The defendant, on the other hand, urges that this court does not have jurisdiction to consider and determine the status of the drugs in question, that the F.D.A. has primary and exclusive jurisdiction with appeal to the circuit court. That contention is likewise without merit. There is no doubt that the F.D.A. does have primary jurisdiction to make determinations concerning the safety and effectiveness of new drugs. Its expertise is necessary for consideration of the complex and technical nature of the factual issues to be evaluated.[6] That question is not, however, in dispute in this instance. The contention urged by the plaintiffs that its drugs are old or grandfathered, must turn upon the court's conclusion as to whether among qualified experts there was general recognition of the safety and efficacy of the drug. [*United States* v. *"Quick-O Ver"*, 274 F. Supp. 443 (1967)]. Counsel for the defendants acknowledged that the fact that the drugs were old or grandfathered would be a defense to be raised and considered in the district court when and if the F.D.A. sought sanctions against the plaintiff manufacturers.

The remaining question regarding the jurisdiction of this court is whether the action for declaratory judgment may be maintained in its present posture. The opinions of the Supreme Court in *Abbott Laboratories* v. *Gardner*, 387 U.S. 136 (1967) and *Toilet Goods Asso.* v. *Gardner*, 387 U.S. 158 (1967) convince this court that the present matter is properly before it. As pointed out in those cases, there is nothing in the Food, Drug, and Cosmetic Act [21 U.S.C. § 301, *et seq.*] which bars a pre-enforcement suit under the Ad-

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[6] See e.g Far East Conference v. United States, 342 U.S. 570 (1952); Tyler Pharmacal Dist. v. H.E.W., 408 F. 2d 95 (7th Cir. 1969); Lemmon Pharmacal Co. v. Richardson, C.A. 68-921, E.D. Pa. 1970.

ministrative Procedure Act [5 U.S.C. §§ 701–704] and the Declaratory Judgment Act [28 U.S.C. § 2201]. The language in the Secretary's announcement of May 20, 1970, of which the plaintiffs complaint and pursuant to which the Secretary apparently intends to proceed against them, is apparently final within the meaning of 5 U.S.C. § 704. (*Abbott,* supra, at 692) The letter of the F.D.A. set out above in note 4, indicates that action against the plaintiffs is imminent. The affidavits of the plaintiffs show that the threatened action will result in substantial injury to them. Therefore, this matter is properly before this court and the defendant's motion to dismiss is denied.

The court indicated above that the F.D.A. has jurisdiction to determine whether the drugs in question are new drugs. The court is of the opinion that, even though that determination can be made in this forum, the nature of the proof relevant to that issue makes the F.D.A. the more able arbiter of the question. However, if such determination is to be binding upon the plaintiffs in this action and the industry in general, parties interested in the status of drug combinations must be given an opportunity to be heard. They must be provided a day in court on the issue, during which a record can be made, on which record appeal to the circuit court can be had. That procedure would produce a resolution to the question which would bind the industry and remove the issue from subsequent, and perhaps numerous, enforcement actions. These plaintiffs quite properly point out that they have as yet had no opportunity to be heard on the question of whether their products are new drugs within the meaning of the Act; and it does not appear that such hearing could have been required of the F.D.A. by the plaintiffs. Evaluation of conflicting reports as to the reputation of drugs among experts

in the field is not a matter well left to a court without chemical or medical background. The court's opinion in this regard has influenced it considerably in its consideration of appropriate temporary relief.

The area of regulation of drugs is one which the court enters with great reluctance. However, the affidavits of the plaintiffs convince the court that they may suffer substantial business losses, perhaps unnecessarily, if the court refuses to grant temporary relief. As the court understands the record before it and the argument of counsel, there is no contention that the use of the plaintiffs' drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs. The court's order, being based upon this hypothesis, will be vacated upon a sufficient contrary showing by the defendant and, upon request by the defendant, the court will arrange to hear its proof in that regard.

The situation revealed by the record to date convinces the court that the status quo must be preserved until such time as the plaintiffs have an opportunity to be heard on the merits of their contention. Therefore, the court will enjoin the defendants from instituting actions against the plaintiffs on account of such of their products as are presently marketed, as contain combinations of pentylenetetrazol and nicotinic acid, are distributed by prescription, and are for treatment

of symptoms of senility in geriatric patients; and the defendants are hereby enjoined from instituting any action against the plaintiffs herein for the cause stated above until such time as there has been a determination that the products in question are new drugs. Recognizing the desirability of the F.D.A.'s making such determination, after a hearing of the matter, this court will defer further proceedings herein upon a showing by the defendants that such hearing will be held. It will dissolve the injunction herein ordered, and dismiss the presentation upon resolution of the question by the F.D.A. after a hearing.[7] Should the F.D.A. decline to hold such hearing, the matter must proceed to determination in this court.

And *It is so ordered.*

Robert W. Hemphill
Robert W. HEMPHILL,
United States District Judge.

COLUMBIA, SOUTH CAROLINA.
FEBRUARY 10, 1971.

[A true copy.
Teste: Miller C. Foster, Jr. Clerk, by: Deputy Clerk.]

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[7] A court has considerable discretion in proceeding in actions for declaratory judgment, and may dismiss such actions if they are pending in litigation elsewhere. Abbott Laboratories v. Gardner, 387 U.S. 136, 155 (1952).

APPENDIX D

The Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040, as amended by the Harris-Kefauver Act, 76 Stat. 780, 21 U.S.C. 301 *et seq.* provides in part:

Section 201(p)(1) (21 U.S.C. 321(p)(1)):

> The term "new drug" means—(1) Any drug * * * the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this chapter it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use;

Section 505(a) (21 U.S.C. 355(a)):

> No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) of this section is effective with respect to such drug.

Section 505(d) (21 U.S.C. 355(d)):

> If the Secretary finds, after due notice to the applicant * * * and giving him an opportunity for a hearing * * * that * * * (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is repre-

sented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof * * * he shall issue an order refusing to approve the application. * * * As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Section 505(e) (21 U.S.C. 355(e)):

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds * * * (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof * * *.

Section 505(h) (21 U.S.C. 355(h)):

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of

Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. * * *.

Section 107(c) of Public Law 87-781, 76 Stat. 788-789, note following 21 U.S.C. 321 (1970 ed.), provides in pertinent part:

* * * * *

(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date [October 10, 1962] by virtue of paragraph (2) of this subsection—

* * * * *

(B) clause (3) of the first sentence of section 505(e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application * * * until * * *: (i) the expiration of the two-year period beginning with the enactment date * * *.

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (c) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when inteneded solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No.

USV PHARMACEUTICAL CORPORATION, PETITIONER

v.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

USV Pharmaceutical Corporation petitions for a writ of certiorari to review the judgment of the United States Court of Appeals for the Fourth Circuit in this case.

OPINIONS BELOW

The opinion of the Court of Appeals (App. A, *infra,* pp. 1a-10a) is reported at 461 F.2d 223. The opinion of the United States District Court for the Eastern District of Virginia (App. D, *infra,* pp. 13a-16a, see also App. E and F, *infra,* pp. 17a-19a), not officially reported, has been reprinted at CCH Food Drug Cosm. L. Rep. ¶ 40,489.

JURISDICTION

The judgment of the Court of Appeals was entered on May 24, 1972 (App. B, *infra,* p. 11a). A petition for rehearing filed by USV was denied on July 5, 1972 (App. C, *infra,* p. 12a). The Chief Justice extended the time within which to file a petition for certiorari until October 30, 1972. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

QUESTIONS PRESENTED

The 1962 amendments to the Federal Food, Drug and Cosmetic Act of 1938 expanded the statutory definition of "new drugs", for which a new drug application must be approved by the Food and Drug Administration in advance of marketing, to include drugs "not generally recognized as *** effective ***" in addition to those "not generally recognized *** as safe ***". A "grandfather" provision, however, exempted drugs already on the market which were not "new drugs" as defined by the Act prior to amendment, and "not covered by an effective [new drug] application ***".

The questions are:

1. Whether the "grandfather" provision applies to pre-1962 drugs which had been the subject of a new drug application ("NDA") when first introduced, but which by the time of the amendments were concededly no longer "new drugs", and were no longer treated either by the manufacturer or by FDA as subject to the regulatory scheme applicable to NDA'd products.

2. Whether the "grandfather" provision is inapplicable to pre-1962 drugs which were never "new drugs" from the moment of their introduction and were never the subject of a new drug application, therefore literally qualifying for "grandfather" protection, merely

because they include the same principal ingredient as earlier products of the same manufacturer for which NDA's had originally been filed.

STATUTES INVOLVED

Pertinent provisions of the Federal Food, Drug and Cosmetic Act of 1938, § 201(p), 52 Stat. 1041, and of the Act as amended in 1962, Publ. L. No. 87-781, 76 Stat. 780, § 102(a)(1), 21 U.S.C. § 321(p)(1), and § 107(c)(4), 21 U.S.C.A. note following § 321, are set out in Appendix I, *supra,* pp. 50a-53a.

STATEMENT

1. During 1955 and 1956 the Commissioner of Food and Drugs approved three new drug applications ("NDA's") covering seven drug products of petitioner USV Pharmaceutical Corp. containing citrus flavonoid compound (App. A, *infra,* p. 2a). The recommended use of the products, as found by the District Court (App. D, *infra,* p. 16a), was control of abnormal capillary permeability and fragility.[1]

Under the statutory scheme then in effect, such prior Food and Drug Administration approval was required before marketing a "new drug", that is, a drug "not generally recognized by experts *** as safe" for its intended uses.[2] In the NDA, the manufacturer was re-

[1] This is a condition of the capillary walls which may result in easy surface bleeding such as in bruises (Transcript of Trial, pp. 288-89). The use of USV's bioflavonoid products for this purpose is recommended to physicians only. While no prescription is required to purchase these products, they are described merely as "a supplementary source of bioflavonoids" in the labeling made available to the lay purchaser (J.A. 187) ("J.A." refers to the Joint Appendix in the Court of Appeals).

[2] Federal Food, Drug, and Cosmetic Act of 1938, § 201(p)(1), 52 Stat. 1041.

quired to show that his product was in fact safe, and approval by FDA of the application constituted the agency's ratification of such proof.[3]

In 1957, USV developed two new bioflavonoid products ("Bivam" and "Duo-CVP with Vitamin K") similar in composition and labeling to the seven products for which new drug applications had been approved the previous year.[4] First obtaining specific advance advice from FDA that Bivam[5] was "generally recognized as safe" (GRAS), and hence not a "new drug", USV placed these "me-too" products on the market without filing NDA's.[6] At no time thereafter did FDA ever assert that either required an NDA.[7]

On February 28, 1961, satisfied that its bioflavonoid products previously covered by NDA's also were by then generally recognized as safe, USV sought an express FDA ruling that these products were no longer "new drugs".[8] In response, FDA advised the company on April 19, 1961 that two of the previously-NDA'd products "are not new drugs". As to the remainder, FDA said it had incomplete current marketing information to make a determination, but would

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[3] § 505(d), 52 Stat. 1052.

[4] App. D, *infra*, p. 15a. No additional labeling directed to physicians, recommending the product for abnormal capillary permeability and fragility, was disseminated for Bivam.

[5] No separate ruling was sought on Duo-CVP with Vitamin K.

[6] App. A, *infra*, p. 8a. In FDA regulatory parlance, a "me-too" product is one substantially identical to a previously-marketed product for which a new drug application has been approved but which subsequently became "generally recognized * * * as safe" (and, since 1962, effective), with the result that the copy is not a "new drug" and can therefore be marketed without an approved NDA. See App. A, *infra*, p. 7a.

[7] See J.A. 150.

[8] J.A. 33-34.

be "pleased" to rule upon receipt of the additional data.[9]

USV supplied such information within a month, noting its "recollection" that "a short time after the NDA became effective" (*i.e.*, in 1956-1957), the products "were no longer considered to be new drugs", and requesting FDA's "confirmation of the above".[10] FDA never responded.

It has traditionally been considered the responsibility of the manufacturer to decide, subject to severe penalties if he is later held to have decided incorrectly, whether his product is a "new drug" requiring premarketing approval by FDA.[11] Because the identical citrus flavonoid compound is contained in all USV bioflavonoid products, three of which FDA had expressly ruled were not "new drugs", USV concluded that the "not-new" status of all these products had been established, and thereafter discontinued filing with FDA the continuing reports and supplemental information required for NDA'd products.[12] Although FDA was thus fully aware of USV's position that the products were no longer "new drugs" within the meaning of the statute and that the company was treating each of them as no longer subject to the regulatory scheme applicable to NDA'd products, at no time was this challenged by the agency.

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[9] J.A. 35-36, 148.

[10] J.A. 37.

[11] *Bentex Pharmaceuticals, Inc.* v. *Richardson*, 463 F.2d 363 (4th Cir. 1972), App. G, *infra*, p. 22a, *petition for certiorari filed*, No. 72-555, October 5, 1972. See also Peter Barton Hutt, *Proper Classification of Products Under the Federal Food, Drug, and Cosmetic Act*, p. 3 (unpublished paper presented at Annual Convention of the Federal Bar Ass'n, Miami, Fla., Sept. 4, 1969).

[12] App. D, *infra*, p. 15a. The requirements then applicable were published at 25 Fed. Reg. 12595 (1960).

2. In 1962, the Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act were enacted, expanding the definition of "new drug" to cover drugs not generally recognized by experts as "safe *and effective*" for their intended uses.[13] However, as to certain products generally recognized as safe prior to 1962, a "grandfather clause" contained in Section 107(c)(4) of the amending statute granted full exemption from the added efficacy element in the definition of "new drug", and preserved their right to remain on the market without advance FDA approval. To qualify for the § 107(c)(4) exemption, it must be shown that the product "on the day immediately preceding the enactment date" (*i.e.*, October 9, 1962) satisfied three conditions: (A) that it was commercially used or sold in the United States, (B) that it was not a new drug as defined in the Act as then in force (*i.e.*, was "generally recognized *** as safe"), and (C) that it was not "covered by an effective [new drug] application" under the Act.

Exemption from the expanded FDA preclearance requirement does not mean, of course, that the public is unprotected against false claims of efficacy for the drug in question. Untrue efficacy claims constitute "misbranding" in violation of the Act,[14] and subject the manufacturer to severe criminal and civil sanctions as well as seizure of the product and its removal from the market.[15]

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[13] Drug Amendments of 1962, § 102(a)(1), (2), *amending* Federal Food, Drug, and Cosmetic Act of 1938, § 201(p), 21 U.S.C. § 321(p).

[14] § 502, 21 U.S.C. § 352.

[15] *Bentex Pharmaceuticals, Inc.* v. *Richardson*, note 11 *supra*, App. G, *infra*, pp. 25a-26a.

The 1962 amendments also expanded the grounds upon which approval of an NDA could be denied or withdrawn by FDA. Prior to 1962, approval could be denied, and once granted could subsequently be revoked, only for insufficient evidence of safety. The 1962 amendments required FDA, in deciding whether to approve or revoke approval of new drug applications, to consider the evidence of efficacy as well. At any time after the expiration of a two-year "grace period",[16] moreover, FDA could initiate revocation proceedings as to pre-1962 NDA's which were still operative and, after "due notice and an opportunity for hearing to the applicant", withdraw approval previously granted upon a finding "that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have * * *".[17]

In July 1968, relying upon an adverse report on the efficacy of one of USV's bioflavonoid products rendered by the National Academy of Sciences/National Research Council Drug Efficacy Study which FDA had commissioned following the 1962 amendments, FDA initiated proceedings to revoke approval of the three bioflavonoid NDA's held by USV.[18] In light of FDA's prior position with regard to the products, however, the company believed that each of its bioflavonoid formulations satisfied the criteria for "grandfather" status under the 1962 amendments to the definition of "new drug", and that under the pre-1962 definition the products were not "new drugs". USV therefore

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[16] Drug Amendments of 1962, § 107(c)(3), 76 Stat. 788-89, 21 U.S.C.A. note following § 321.

[17] Drug Amendments of 1962, § 102(d), 76 Stat. 782, *amending* Federal Food, Drug, and Cosmetic Act of 1938, § 505(e), 21 U.S.C. § 355(e).

[18] J.A. 28, 30-31.

instituted the present action in the District Court for a declaratory judgment against the Secretary of Health, Education and Welfare and the Commissioner of Food and Drugs, who are charged with the administration of the Food, Drug and Cosmetic Act, which would confirm USV's right to continue to market the products even without an approved new drug application. A stay of the administrative revocation proceeding for the pendency of the declaratory judgment action was sought from FDA.[19]

3. The District Court (App. D, *infra*, pp. 13a-16a) rejected FDA's challenge to its jurisdiction (p. 14a) and, proceeding to the merits, held that USV was correct as to *all* its bioflavonoid products—those for which NDA approval had been granted when originally introduced as well as those "me-too" products for which no NDA had ever been filed. The court found Clauses (A) and (B) of § 107(c)(4) to be satisfied (*id.*, pp. 14a, 15a-16a; App. F, *infra*, p. 18a). It further found that,

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[19] The stay was denied, but no further action was taken by FDA to prosecute the revocation proceeding. In July 1970, contemporaneously with the setting of a trial date in the declaratory-judgment action, FDA sought to revive the revocation proceeding by calling upon USV to establish its right to a hearing under "summary judgment" regulations which the agency had promulgated in the interim. USV again moved for a stay pending disposition of the declaratory-judgment action (J.A. 39-41). Eight days before trial in the district court was scheduled to begin, FDA denied the stay and entered a final order of revocation, refusing to allow USV to contest the matter further (J.A. 42). The revocation order has since been set aside by the Court of Appeals for the District of Columbia Circuit for denial of "administrative due process", resulting from FDA's use of procedures which were "fundamentally defective • • • unsound and unfair" (*USV Pharmaceutical Corp.* v. *Secretary of HEW*, No. 24900, decided August 14, 1972, App. H, *infra*, pp. 46a, 48a). The Government has informed USV that "after reviewing the decision of the court in this matter, we have concluded not to seek certiorari" (Letter dated Oct 17, 1972 from Peter Barton Hutt, Esq. to Joel E. Hoffman, Esq.).

as a result of the actions of USV and of FDA's administrative treatment of the matter between the time USV filed its new drug applications and the enactment of the 1962 amendments, in which neither the manufacturer nor the agency treated the products as subject to the regulatory scheme applicable to NDA'd products, the previously-approved NDA's had been effectively withdrawn by USV in a practical sense prior to October 1962; hence "none of the plaintiff's bioflavonoid products in question were covered by an effective NDA as of October 9, 1962" (*id.*, p. 15a). Clause (C) of § 107(c)(4) was thus satisfied and the pre-amendment definition of "new drug" continued to apply under which the products were not "new drugs" (*ibid.*). The remedy for any untrue claims of efficacy, the District Court concluded, thus continued to be in criminal, injunction and seizure actions for unlawful "misbranding", rather than in administrative denial or revocation of marketing authority by FDA.

On appeal, after summarily affirming the jurisdictional ruling below,[20] the Court of Appeals considered separately the NDA'd and non-NDA'd drugs. Although both groups were found to satisfy Clauses (A) and (B) of § 107(c)(4), the court rejected the District Court's finding that the NDA's "had been effectively and practically withdrawn and that accordingly the

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[20] App. A, *infra*, p. 2a. The Court of Appeals invoked by reference the rationale it had set out in the companion case of *Bentex Pharmaceuticals, Inc.* v. *Richardson*, note 11 *supra*, App. G, *infra*. The Government's pending challenge to that decision thus necessarily calls into question the jurisdiction of the lower courts to decide the merits of the present case. See especially p. 18 n. 15 of the Solicitor General's Petition for Certiorari in *Bentex* (No. 72-555), which seems implicitly to take issue with the jurisdictional ruling here. That ruling is apparently also in conflict with *Ciba Corp.* v. *Richardson*, 463 F.2d 225 (3d Cir. 1972), *petition for certiorari filed*, No. 72-528, Oct. 2, 1972.

drugs were not covered by an effective NDA" on October 9, 1962 (App. A, *infra,* p. 4a).

"The error in this reasoning", the court below stated, "is that it assumes that a manufacturer may effect a withdrawal of an effective NDA, either by a formal notice or by discontinuing compliance with the reporting requirements for NDA'd drugs. * * * [H]e has no such right after approval of the application by the Secretary. At that point, only the Secretary can withdraw the approval". (App. A, *infra,* pp. 4a-5a.) Thus, in the view of the Court of Appeals, the District Court erred in finding that there had been a practical and effective withdrawal of the new drug applications by USV; no such action was permitted under the law and, since the Secretary had undertaken no action to withdraw *approval* of the applications, the products were still covered (*id.,* p. 5a).

The Court of Appeals additionally rejected an alternative theory which it found implicit in USV's argument: that since all the products involved had concededly become "generally recognized * * * as safe" prior to October 9, 1962, they had ceased to be "new drugs" and therefore the "previously issued NDA's were no longer needed or 'effective' ". This theory, the court said, "would make surplusage of requirement (C) in the exemption statute" and by thus treating (C) as a "nullity" would offend "the well settled rule of statutory construction that all parts of a statute are to be given an effect if at all possible". (*Id.,* pp. 5a-6a.)

The court acknowledged that a separate problem existed as to USV's two non-NDA'd "me-too" products. Facially, they were exempt under the plain language of § 107(c)(4) since they were admittedly "generally recognized *** as safe" from the outset and had *never* been "covered" by an effective NDA (*id.,* p. 6a).

Moreover, most commentators, while admitting the "incongruity" of a result which would exempt "me-too" products but not their pioneer NDA'd products, considered the result "compelled by the literal language of the statute". FDA's contention to the contrary in the course of this litigation had already been "severely criticized and with considerable reason". The argument was "at variance with the uniform position [FDA] has taken over the years with regard to the nature of NDA's", which, simply stated, was that the NDA is "personal" to drugs "as individual articles, not as collective groups". (*Id.*, p. 8a.)

Yet, having thus accepted the argument for exempting "me-too" drugs generally, the Court of Appeals nevertheless ruled that USV's "me-too's" were not entitled to the exemption. The company's "me-too's" were "similar in formula and labeling" to its NDA'd drugs; these NDA's were "personal" to USV; thus, the court reasoned, they covered not only the specific NDA'd products but also "all others like in formula". And, since the NDA'd products were disqualified, the two non-NDA'd products must derivatively fall. The court conceded that "this conclusion places [USV] in a less favorable position than [other manufacturers] who may have copied its product prior to October 9, 1962", but the inequity created by its decision could only be redressed, it held, by Congress. (*Id.*, p. 10a.)

REASONS FOR GRANTING THE WRIT

The decision of the Court of Appeals in this case presents questions of large importance in the administration of the Food, Drug and Cosmetic Act, relating to the legal scope and practical application of the "grandfather" provision contained in the 1962 amend-

ments. Definitive and prompt resolution of these issues, which can come only from this Court, is required in the interest of orderly and manageable enforcement of the Act. Review by this Court would remove the existing confusion and uncertainty surrounding this problem, would obviate further litigation, and would be helpful both to FDA, which must administer the statute in accordance with Congress' intentions, and to manufacturers who must know what the statute means in order to comply with it.

1. *The Importance of the Issues.* In attempting explicitly to delineate the precise circumstances in which the various 1962 drug amendments would apply to products already on the market, Congress demonstrated its judgment that the new classification criteria, testing requirements, burdens of proof, and reporting obligations were inappropriate for blanket retroactive imposition. Yet ever since enactment of the 1962 amendments the complex language of § 107(c)(4)'s "grandfather" provision has made its application confused and uncertain.

In straining for a simple and superficially equitable approach, however, the decision below improperly ignores the balance struck by Congress, disregarding this Court's admonition that "in our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop" (*62 Cases of Jam* v. *United States,* 340 U.S. 593, 600 (1951)).[21] Nor has even-handed enforcement of the Act been simplified; the Court of Appeals' decision, if unreviewed, would leave § 107(c)(4) in even greater

[21] See also *United States* v. • • • *Decholin,* 264 F.Supp. 473, 480, 482-83 (E.D. Mich. 1967).

disarray for the future. The right to market a range of concededly safe pre-1962 drugs remains unresolved; the administrative processes of FDA are burdened, despite the agency's repeated protests that its statutory duties exceed its resources; and manufacturers such as USV, who prior to 1962 expended their energies and resources to develop and market new drugs under FDA's complex NDA procedures, are forever saddled with expensive and burdensome restrictions despite the fact that the drugs are now generally recognized as safe, while others are forever exempted who simply copied the products of such innovative firms.

The number of long-marketed drugs affected by the decision below, although difficult to estimate precisely, is undoubtedly large. New drug applications for approximately 7,100 products were approved by FDA between 1938 (when the Food, Drug and Cosmetic Act became law) and 1962.[22] FDA advised Congress in 1969 that about 1,000 of these were contended by their manufacturers to have become "generally recognized *** as safe", and thus no longer "new drugs", in the years between approval of the NDA and 1962.[23] It would be conservative to assume that in at least a substantial number of these instances the manufacturers accordingly ceased compliance (as did USV) with the reporting and approval requirements applicable to "new drugs". The number of "me-too" copies involved may be as high as 13,000, if the Government is correct that an average of some 13 copies for which no NDA was

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[22] See Solicitor General's Petition for Certiorari, p. 5, *Richardson* v. *Bentex Pharmaceuticals, Inc.*, No. 72-555, filed Oct. 5, 1972.

[23] *Hearings on Drug Efficacy Before a Subcommittee of the House Committee on Government Operations*, 91st Cong., 1st Sess. 375 (1969).

ever approved are now being marketed for each drug NDA'd prior to 1962.[24]

The substantive issues decided below, no less than the threshold jurisdictional and procedural issues in the companion cases before the Court,[25] are thus "of great importance to the Food and Drug Administration and the drug industry * * *" (Solicitor General's Petition for Certiorari, p. 20, No. 72-394 (*Hynson*)). Unless these substantive issues are settled now, extensive further litigation in the lower courts will inevitably ensue. Plenary review by the Court at this time is plainly warranted.[26]

2. *The Error as to Previously-NDA'd Products.* The District Court found that USV's actions subsequent to approval of its original NDA's—affirmed or ac-

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[24] Solicitor General's Petition for Certiorari, pp. 16-17 n. 14, *Richardson* v. *Bentex Pharmaceuticals, Inc.*, No. 72-555, filed Oct. 5, 1972.

[25] *Richardson* v. *Hynson, Westcott & Dunning, Inc.*, No. 72-394, *petition for certiorari filed*, Sept. 7, 1972; *Hynson, Westcott & Dunning, Inc.* v. *Richardson*, No. 72-414, *petition for certiorari filed*, Sept. 11, 1972; *Ciba Corp.* v. *Richardson*, No. 72-528, *petition for certiorari filed*, Oct. 2, 1972; *Richardson* v. *Bentex Pharmaceuticals, Inc.*, No. 72-55, *petition for certiorari filed*, Oct. 5, 1972.

[26] The manufacturer's cross-petition for certiorari in the *Hynson* case (No. 72-414) seeks to raise, *inter alia*, the issue here presented as to products which once were covered by a new drug application. Unlike the products involved in *Hynson*, however, USV's bioflavonoid products have been the subject of a full evidentiary trial on the questions (a) whether the factual prerequisites to exemption from the change in the definition of "new drug" are met, and (b) whether the products are in fact "new drugs" under the definition prior to amendment. Regardless of the Court's decision to grant or deny the petition in No. 72-414, therefore, we submit that the issues raised by the instant petition for certiorari are both ripe and properly presented.

quiesced-in by FDA—amounted in practical terms to withdrawal of the NDA's prior to October 9, 1962. Thus, *a priori,* they could not on that date have been "covered by an effective application" and § 107(c)(4)'s third criterion for "grandfather" exemption was met.

The Court of Appeals disagreed. There was no provision in the statute for an applicant's "withdrawal" of an NDA once approved; the only "withdrawal" contemplated was withdrawal of approval by FDA, under the authority of § 505(e), and here approval had not been withdrawn. Thus, the court concluded, the products remained "covered" by effective NDA's on the date of the new statute.

But the court's preoccupation with whether USV had the "right" to "withdraw" its NDA misconceives the critical inquiry. Regardless of how the District Court had formulated the issue, the question on appeal was not whether USV had withdrawn its NDA, or indeed even whether USV had a right to "withdraw". Properly stated, the only question was whether USV's bioflavonoid products which had earlier been NDA'd were, on October 9, 1962, still "covered by an effective [new drug] application".

The District Court relied upon the sequence of events between the time of the filing of these NDA's and the 1962 amendments for its finding of practical and effective withdrawal of the NDA's prior to October 9, 1962, and on this basis concluded that thereafter the products were no longer "covered". In its preoccupation with the abstract question whether USV lawfully could "withdraw" its NDA, the court below ignored the underlying facts found by the District Court, which showed that by 1962 the products involved

were no longer being treated by either the manufacturer of FDA as subject to the regulatory scheme applicable to NDA'd products. These facts, we submit, surely justified the District Court's ultimate conclusion thaton October 9, 1962, the products were no longer "covered" by an effective NDA.[27]

Nor is the Court of Appeals' contrary ruling supported by § 505(e), the sole authority discussed in the opinion. In essence, the court said, once a product is NDA'd, it is forever NDA'd—unless FDA itself withdraws approval of the NDA under § 505(e). But, as the court itself recognized in upholding the jurisdiction of the District Court to entertain this action, FDA is wholly without authority to consider or decide in approval-revocation proceedings under § 505(e) whether a product previously approved continues to be a "new drug",[28] and that issue cannot be raised by either party in a § 505(e) proceeding. That provision cannot be invoked to terminate NDA coverage on the ground that the product has become GRAS and therefore is no longer a "new drug" requiring the regulatory oversight imposed on NDA'd products. Section 505(e) is a pro-

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[27] The District Court found (App. D, *infra*, pp. 14a-15a):

"The plaintiff made that clear through its correspondence with the Federal [sic] Drug Administration. It then ceased compliance with the submittal of data and new labeling, as required by the Federal Drug Administration for products covered by effective NDA's—The record further discloses that the Federal Drug Administration advised the plaintiff in writing that its products covered by [two of the NDA's] were not new drugs—and it was stipulated that the compound in these two products is identical to the bioflavonoid compound in plaintiff's other products and that the recommended uses of all of the [bioflavonoid] products are essentially the same."

[28] The court's rationale was elaborated in the companion case of *Bentex Pharmaceuticals, Inc.* v. *Richardson*, note 11 *supra*, App. G, *infra*. The Solicitor General is petitioning for certiorari to review that ruling (No. 72-555), which is also challenged in *Hynson, Westcott & Dunning, Inc.* v. *Richardson*, No. 72-414, *supra*.

vision of limited scope, permitting FDA to withdraw approval of an NDA only for the very opposite reason —that the evidence no longer shows the product to be safe (or, under the new statute, effective) and hence no longer allows the product to be marketed.

Perhaps misled by its assumption that the abbreviation "NDA" stands for "New Drug *Approval*" rather than for "New Drug *Application*" (see *Bentex Pharmaceuticals, Inc.* v. *Richardson*, note 11 *supra*, App. G, *infra*, p. 21a n.2), the court below nevertheless confused "withdrawal" *of the NDA*, as found by the district court, with "withdrawal *of approval*", as provided for in § 505(e). But § 505(e) does not, as we have shown, prescribe the procedures for terminating coverage of an NDA because the drug involved has become generally recognized as safe (or, since 1962, effective) and need no longer be subject to NDA regulation. So the fact that FDA never revoked approval of the NDA's involved in this case by proceeding under § 505(e) is simply irrelevant.

If an approved NDA which has become superfluous may be retired on that ground (and common sense says it may and should), then the procedure for doing so must be inferred from the whole scheme and purpose of the statute. And it strains both reason and common sense to hold that though the GRAS status of a product has been asserted by the manufacturer, ratified by FDA, acted upon by the manufacturer (in discontinuing all NDA reports) and acquiesced-in by FDA (in no longer imposing NDA controls), the product is nevertheless still "covered by an effective [new drug] application" because there has been no resort to the formal revocation-of-approval procedures of § 505(e), which can be initiated only by FDA, extend only to the precisely opposite situation, and therefore could not have been invoked by USV to terminate the coverage of its NDA's on the ground that the products were no longer "new".

However characterized, the nub of what happened here was that through the actions of both USV and FDA, taken together, the NDA's were inactivated and the products involved became no longer "covered by an effective [new drug] application". Thus, plainly, the products satisfied the requirement of Clause (C) in § 107(c)(4) that they were not "covered by an effective [new drug] application" on October 9, 1962.

Nor, finally, does this conclusion make "surplusage" of Clause (C), as the court below suggested. The fact that an NDA'd product has become GRAS and no longer "new" does not, standing alone, automatically inactivate the NDA. Obviously there must be some further action which removes the product from new-drug regulation, before it can be found the product is no longer "covered" by an effective NDA. Here, however, FDA not only ruled that the products were GRAS, and thus "not new", but unambiguously acquiesced in USV's withdrawal of these products from new-drug regulatory procedures. FDA's own actions in connection with those of USV established that the products were no longer "covered". According to the District Court it was necessary for USV to show these additional facts in order to satisfy the criterion for exemption prescribed by Clause (C). Under no view of the statute as interpreted and applied by the District Court, therefore, can Clause (C) be considered surplusage.

3. *The Separate Error as to "Me-Too" Products.* Two of USV's bioflavonoid products had never been the subject of new drug applications, and had been marketed from the outset on the basis of USV's conclusion (and in one case FDA's as well) that they were not "new drugs". The opinion below "made clear" (Solicitor General's Petition for Certiorari, p. 16 n. 13, No. 72-555 (*Bentex*)) that "me-too" products generally are exempted by the "grandfather" clause, but then con-

cluded it would be inequitable to permit USV's "me-too" products a more generous treatment than their NDA'd predecessors. This result, the court conceded, "places [USV] in a less favorable position than that occupied by others who may have copied its product" and who, under the statute, are plainly entitled to "grandfather" protection. But that "inequity" inheres in the law, the court suggested, and "may only be redressed by Congress, not by the Courts under the guise of construction".

The Court of Appeals correctly analyzed the legal status of "me-too" products under the statute. But in its apparent unwillingness to allow USV's "me-too's" a more favorable disposition than the same company's pioneering NDA'd products, despite the protection clearly enjoyed by competing tag-along manufacturers, the court produced a result which does violence to the express terms of the statute and which, in fact, compounds inequity.

At the outset, the Court of Appeals acknowledged that USV's "me-too" products are "literally" exempt under the plain language of § 107(c)(4) since they had never been "covered" by an effective NDA, and the agency itself had contemporaneously ruled that prior to 1962 at least three of the products (including specifically one "me-too") were not "new drugs". Moreover, knowledgeable commentators recognized that such a result was "compelled by the literal language of the statute", and even FDA's own General Counsel had "conced[ed] that the position of his agency [to the contrary] was in considerable doubt".[29]

[29] App. A, *infra*, pp. 7a, 9a. Indeed, the recent scholarly commentary repeatedly cited by the court in its opinion asserts: "Ultimately, the issue of the status of 'me-too' drugs will have to be squarely faced, and the FDA interpretation of § 107(c)(4), holding that they follow the pioneer's fate, should be repudiated by the courts". *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown L. Journal 185, 206-07 (1971).

Yet the court would not accept the conclusion to which its own analysis led. To sustain the exemption for the "me-too" products, the court said (App. A, *infra*, p. 7a),

> "creates an inequitable result, provided the pioneer drug was NDA'd. In that event, the pioneer drug would be subject to withdrawal of marketing privilege *** whereas its copy would enjoy immunity from any such requirement under Section 107(c)(4)."

The court's escape from this dilemma of its own creation was through a novel—and, we submit, erroneous—application of the long-established doctrine that an NDA is "personal" to the manufacturer submitting the application and to the drug covered.

USV's new drug applications, being "personal to it", the court held (*id.*, p. 10a),

> "would cover all its products similar in formula, including those specifically described in its applications and all others like in formula. The similarity in formula between [USV's] NDA'd drugs and its 'me-too's' is stipulated. Under those circumstances, both the NDA'd and the 'me-too' drugs will be treated alike and neither can qualify for exemption * * *."

But this ruling—that an NDA radiates out to all similar products of the applicant—contravenes the vital second branch of the rule of personality: the NDA is "personal" not only to the manufacturer but to the specific drug as well. The NDA's approved for USV's original seven bioflavonoid products could not, as a matter of law, cover the two subsequently marketed products as to which no NDA's were ever filed.

FDA has never countenanced the marketing of a new dosage form or combination which was not itself GRAS, merely because the manufacturer had obtained

approval of an NDA for an earlier product involving the same principal ingredient. Nor has the agency ever previously made the argument that such new products were "covered" by the original NDA. Indeed, in 1957 FDA accepted and ruled upon supplemental NDA's covering several other new dosage forms of the product covered by USV's original NDA, without any suggestion that it viewed its action as superfluous. And, in the case of Bivam and Duo-CVP with Vitamin K, the agency plainly considered the products GRAS when introduced, hence "not new" drugs, hence never subject to preclearance through the NDA process, and hence never "covered" by an effective NDA.

We submit that the court below simply ignored the applicable law in an effort to mitigate an inequity of its own creation. That inequity is perceived cannot, however, justify departure from the scheme prescribed by Congress. As Judge Friendly wrote in *Pfizer, Inc.* v. *Richardson,* 434 F.2d 536, 542 (2d Cir. 1970), where the shoe was on the other foot, "a sufficient answer is the simple if not altogether satisfying one that Congress said so".

Indeed, to accept the conclusion of the Court of Appeals is to heighten, rather than mitigate, any inequity inherent in the law. Under the decision below:

— Pre-1962 NDA'd products which during that period became GRAS, would not be exempt;

— Even pre-1962 "me-too" products of the same manufacturer, although always GRAS, and never covered by an NDA, would not be exempt;

— Yet "me-too" products of other manufacturers, who had not invested the industry and resources required to obtain an NDA, but simply

piggy-backed on the effort of the pioneering manufacturer, would be exempt.

These anomalies can in fact be avoided, while still remaining faithful to the statute as enacted, by validating USV's primary contention as to the exempt status of its NDA'd products so as to produce a result which is equitable and consistent across the entire range of USV's bioflavonoid products. If, as we contend, the NDA'd products were not "covered" by effective NDA's on October 9, 1962—and this conclusion would seem to follow ineluctably from the course of dealings between FDA and USV during the years 1957-1962—then the pioneering NDA'd products are plainly qualified for the "grandfather" exemption of Section 107 (c)(4), along with the "me-too" products which were never "covered", and no inequity results.

But even if our position on the formerly NDA'd products is rejected, we submit, this Court should reinstate the applicability of the "grandfather" clause as Congress has written it to USV's "me-too" products, so as to avoid the even more arbitrary and illogical discrimination engrafted onto the statute by the court below.

CONCLUSION

Fair and effective application of the "grandfather" provision of the 1962 amendments to the Food, Drug, and Cosmetic Act has been seriously impaired by the decision of the Court of Appeals in this case. Unless reversed by this Court, the decision below will create great uncertainty and confusion both for the Food and Drug Administration in administering the statute and for manufacturers in complying with it. Further review is warranted not only by the impor-

tance of the issues and the desirability of obviating extensive and time-consuming further litigation in the lower courts, but by the clear errors of statutory construction and the manifest inequities reflected in the ruling below.

The petition for a writ of certiorari should therefore be granted.

Respectfully submitted,

ROBERT L. WALD,
SELMA M. LEVINE,
JOEL E. HOFFMAN,
Attorneys for Petitioner.

PHILIP ELMAN,
WALD, HARKRADER & ROSS,
Of Counsel.

October 30, 1972

APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

No. 71-1596

USV PHARMACEUTICAL CORPORATION, *Appellee,*

v.

ELLIOT L. RICHARDSON, Secretary of Health, Education, Welfare, and HERBERT L. LEY, JR., Commissioner of Food and Drugs, Food and Drug Administration, *Appellants.*

Appeal from the United States District Court for the Eastern District of Virginia, at Alexandria. Oren R. Lewis, District Judge.

(Argued December 8, 1971. Decided May 24, 1972.)

Before WINTER, RUSSELL and FIELD, Circuit Judges.

Howard S. Epstein, Attorney, Department of Justice, (Richard W. McLaren, Assistant Attorney General, Bruce B. Wilson, C. Coleman Bird, and Cheryl S. Karner, Attorneys, Department of Justice, and Peter Barton Hutt, Assistant General Counsel, Joanne S. Sisk, Richard S. Silverman, Attorneys, Food, Drugs, and Environmental Health Division, Department of Health, Education, and Welfare, on brief) for Appellants, and Joel Hoffman (Robert L. Wald, Selma M. Levine, and Wald, Harkrader, Nicholson and Ross on brief) for Appellee.

RUSSELL, Circuit Judge:

Unlike the drug manufacturers in *Bentex,*[1] this plaintiff

[1] *Bentex Pharmaceuticals, Inc.* v. *Richardson,* No. 71-1243 (4th Cir., appeal docketed March 11, 1971).

markets a line of citrus bioflavonoid drugs,[2] of which all but two were covered by NDAs issued at various times in 1955 and 1956. Like the plaintiffs in *Bentex,* however, it seeks by an action for declaratory judgment to secure the benefit of the exemption available under the "grandfather clause"[3] from the enlarged definition of a "new drug" included in the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act of 1938. The defendants, who are the Secretary of Health, Education and Welfare (hereinafter referred to as HEW) and the Commissioner of the Food and Drug Administration (hereafter referred to as Commissioner), urge that jurisdiction should be refused on two grounds: 1. Primary jurisdiction lies with HEW; and 2. Failure to exhaust administrative remedies. They, also, attack the right of the plaintiff to claim the exemption. The District Court sustained jurisdiction and, largely on the basis of a Stipulation of Facts, upheld plaintiff's right to the statutory exemption both for its NDA'd and its non-NDA'd drugs. We reverse.

The threshold question raised by the defendants and overruled by the District Court may be quickly disposed of. Under similar circumstances in *Bentex,* we sustained the right of the District Court to entertain an action for declaratory judgment. We reach the same result here. Since we dismiss the claim of the plaintiff for exemption on behalf of its drugs on substantive grounds, it is unnecessary to consider the additional objection that plaintiff has failed to exhaust administrative remedies.

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[2] "Bioflavonoid" is defined in Dorland's Illustrated Medical Dictionary, 2d Edition, as follows: "a generic term for a group of compounds which are widely distributed in plants and animals and which are concerned with maintenance of a normal state of the walls of small blood vessels." Stipulation of Facts, #4.

[3] Section 107(c)(4), Pub. L. 87-781 (1962), 21 U.S.C., 1972 Supplement, pp. 191-2.

The substantive issue posed by this action is the right of the plaintiff to the exemption provided by Section 107(c)(4) from the revised definition of "new drug" incorporated in the 1962 Amendments. In resolving that issue, we must differentiate, even as the "grandfather clause" itself does, between the plaintiff's drugs, which were covered by an "effective NDA",[4] and those, which were marketed without an NDA. The Act makes a distinction in "grandfather" rights between a drug marketed under an NDA[5] and one marketed without an NDA. In the case of a drug covered by a previously approved NDA, the 1962 Amendments required the Secretary to withdraw the approved NDAs if after notice and opportunity of hearing, the applicant failed to file substantial evidence[6] that the drug previously approved is both safe and effective.[7] For such drugs, however, a grace period or temporary "grandfather right" was granted. Under it, the manufacturer was given two years within which to develop his showing of effectiveness and, during this period, the Secretary was prohibited from withdrawing or suspending the previously granted NDA.[8] On the other hand, a non-NDA'd drug which met the criteria stated in Section 107(c)(4) was exempted permanently from the amended definition of "new drug" made by the 1962 Amendments and was thereby relieved of securing an approved NDA as a condition for marketing clearance. The statutory cri-

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[4] "Effective", as used in this phrase, means simply approved. Hagan, *Grandfather Protection Under the Drug Amendments of 1962*, 19 Food Drug Cosm. L. J., 119, p. 121.

[5] This is the term used to describe an approved preclearance application under Section 355.

[6] "Substantial evidence" is defined in the Act (21 U.S.C. 355 (d)).

[7] Section 355(e), 21 U.S.C.

[8] Section 107(c)(3)(B), 21 U.S.C., note foll. Section 321.

teria for this permanent "grandfather" exemption are stated as "any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined in Section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under Section 505 of that Act".

It is the contention of the plaintiff that all its drugs in question, both those previously NDA'd and those not, are protected by the permanent "grandfather clause" (i.e., Section 107(c)(4)). Because the statute seemingly makes a distinction between the two, it is proper to consider separately the two groups of drugs: i.e., those having NDAs and those without NDAs.

Taking up first plaintiff's NDA'd drugs: There is no dispute that such drugs met criteria (A) and (B), as set forth in the "grandfather clause", but the defendants seriously dispute the claim that they meet condition (C). Facially at least, this contention of the defendants seems unanswerable. These drugs are "covered by an effective application" or NDA, and are thus specifically barred by condition (C) from qualifying for exemption from the application of the effectiveness Amendments of 1962. The District Court found, however, that before "the day immediately preceding the enactment date", which was October 9, 1962, the previously granted NDAs had been effectively and practically withdrawn and that accordingly the drugs were not covered by an effective NDA on the crucial date of October 9, 1962. The error in this reasoning, however, is that it assumes that a manufacturer may effect a withdrawal of an effective NDA, either by a formal notice or by discontinuing compliance with the reporting requirements for NDA'd drugs. While an applicant may, during the pendency of his application, withdraw his application, he has no such right after approval of the application by the Secretary. At that point only the Secretary can with-

draw the approval. As one commentator has accurately summed up, "It is true that a manufacturer may withdraw a pending NDA. Sec. 21 C.F.R. sec. 130.8 (1971). However, no provision in the law permits a manufacturer to withdraw an effective NDA; only the FDA can do so through Section 505(e) procedure".[9] Prior to October 9, 1962, there was in this case no proceeding by FDA under Section 505(e) with reference to plaintiff's NDA'd drugs and there was accordingly no valid withdrawal of the plaintiff's effective NDAs, on or before the enactment date of the 1962 Amendments.

The plaintiff, though, presses another theory upon the basis of which it claims the previously issued NDAs are to be regarded as ineffective on October 9, 1962. Thus it argues that its pre-1962 NDA'd drugs became generally recognized as safe on or before October 9, 1962. So much the defendants seem to concede in the Stipulation of Facts submitted to the District Court. From this fact, it reasons that its NDA drugs ceased to be "new drugs" as defined in the Act, on or before October 9, 1962, and, ergo, its previously issued NDAs were no longer needed or "effective" on the critical date of October 9.[10] The difficulty with this argument, plausible though it may be, is that it would make surplusage of requirement (C) in the exemption statute. Thus, if a drug met the test set up in (B), that is, was generally recognized as safe on October 9, 1962, it would not be necessary, under the plaintiff's argument, to consider whether (C) was applicable or not. Such a construction of the exemption statute, under which a clearly stated condition to its application is to be treated as a nullity, offends the well-settled rule of statutory con-

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[9] Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185 at p. 198, n. 77 (1971).

[10] See Barth, *Following the NAS-NRC Effectiveness Review, What?*, 22 Business Lawyer, 1185, 1187 (1967).

struction that all parts of a statute are to be given effect if at all possible.[11] It is manifestly possible to give effect to the conditions enunciated in both (B) and (C). There are many drugs that satisfy both conditions, that is, are generally recognized as safe and effective and are being marketed without an approved NDA. There is nothing inconsistent in the two requirements. Moreover, condition (C) represented a limitation on the right to an exemption that the Congress clearly and unmistakably intended to apply. The Congress never intended that a drug being marketed under an approved NDA might qualify under the "grandfather clause." This is plain from the comment in the Conference Committee Report that the exemption was to apply "to existing labeling claims of drugs *that have never previously been subject to the new-drug procedure*". (Italics added.) H.R. Rep. 2526, 87th Cong., 2d Sess., p. 23. Moreover, the argument of the plaintiff would run counter to the principle that statutory exemptions, particularly as applied to statutes concerned with public health and safety, are to be strictly and narrowly construed.[12]

The plaintiff has, however, two drugs,[13] involved in this proceeding, which were generally recognized as safe and were[14] marketed as "old drugs" without an approved NDA on October 9, 1962. These drugs, as we earlier indicated, present separate problems from those drugs for which there are approved NDAs. They fall into the category of what are generally described in the trade as "me-

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[11] *Jarecki* v. *G. D. Searle & Co.* (1961) 367 U.S. 303, 307; *Ginsberg & Sons* v. *Popkin* (1932) 285 U.S. 204, 208.

[12] *United States* v. *Allan Drug Corporation* (10th Cir. 1966) 357 F. 2d 713, 718, cert. denied 385 U.S. 899.

[13] Duo-C.V.P. with Vitamin K Capsules and Bivam.

[14] Stipulation of Facts, Number 17.

too" drugs.[15] Such a drug, if generally regarded as safe on October 9, 1962, meets literally the criteria for exemption stated in the "grandfather clause". To sustain the exemption, however, creates an inequitable result, provided the pioneer drug was NDA'd. In that event, the pioneer drug would be subject to withdrawal of marketing privilege absent substantial evidence of effectiveness, whereas its copy would enjoy immunity from any such requirement under Section 107(c)(4). Most commentators, while admitting the incongruity of this result, justify it as one compelled by the literal language of the statute.[16] Their reasoning is similar to that of the Court in *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F. 2d 536, 542, where speaking to a somewhat illogical provision in this same Act, Judge Friendly said: "A sufficient answer is the simple if not altogether satisfying one that Congress said so."[17] The FDA itself has recognized the vexing problem presented by the "me-too" drug and has sought to resolve it by a change in its position on the scope and application of an NDA.

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[15] A "me-too" drug is generally defined as "one which is equivalent to another, pioneer drug, which preceded it on the market." Note, *Drug Efficacy and the 1962 Amendments,* 60 Georgetown L. Journal, 185, at p. 198, n. 78, (1971).

[16] See, Note, *Drug Efficacy and the 1962 Amendments,* 60 Georgetown L. Journal, 185, at p. 203 (1971):

> "Surely, me-too drugs never processed through the new drug procedures satisfy all the requirements of section 107 (c)(4)."

To the same effect is Hagan, *Grandfather Protection Under the Drug Amendments of 1962,* 19 Food Drug Cosm. L.J., 119, at pp. 125-6. D'Andrade, *The Effect of NAS-NRC Review on Me-Too and Post-'62 Drugs,* 25 Food, Drug, Cosm. L.J., 330, 334 (1970).

[17] This, of course, is not the only inequity in the Amendments. There are other inequities, as FDA freely conceded at a House Hearing before a Subcommittee of the Commission on Government Operations on Drug Efficacy, Part 2, 91st Cong., 1st Sess. (1969), pp. 384-5.

It is the contention of the FDA that an approved NDA covers not merely the marketing of the parent but also its "me-too" offsprings and for that reason the "me-too" drugs have been permitted to be marketed without an NDA. Accordingly, under this theory, the withdrawal of the approved NDA of the pioneer operates as a withdrawal of marketing rights for the "me-too", unless the latter, either individually or in conjunction with its pioneer, provides substantial evidence of effectiveness. This view has, however, been severely criticized and with considerable reason. It is, as one critic has observed, "at variance with the uniform position it (FDA) has taken over the years with regard to the nature of NDAs." This position, which is termed the "personal approach" holds that "Section 505 applies to drugs as individual articles, not as collective groups, and that each manufacturer of a new drug must file his own NDA." This critic concludes with the observation that it is "an unjustifiable exercise in semantics to say that a drug legally marketed without an NDA was 'covered' by the NDA of another manufacturer's drug.'"[18]

That the policy of FDA has heretofore been contrary to the position now taken by it is further illustrated by the circumstances under which at least one of the "me-toos" of the plaintiff began marketing. Prior to marketing Bivam, one of its "me-toos" similar in formula to other drugs previously NDA'd by it, the plaintiff inquired of FDA whether it was an "old drug" entitled to be marketed without an NDA. FDA, after reviewing its composition and labeling, advised the plaintiff it was a product "generally regarded as safe" (and thus an "old drug") and could be marketed without an NDA. There was no suggestion by the plaintiff that it sought to market this drug under any previous NDA granted one of its products nor did the FDA base its advice on that basis. Both the

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[18] Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal, 185, at p. 203, n. 111 (1971).

plaintiff and FDA assumed at that time that a "me-too" drug, which had become generally recognized as safe, was entitled to be marketed without an NDA; in short, that the qualification for marketing a "me-too" drug was general recognition of safety and not the NDA of its pioneer.

It would seem that the consistent construction of the Act by the FDA for thirty years[19] and a construction which accords with the literal language of the Act itself may only be changed by Congress itself.[20] In fact, the General Counsel of FDA, in testimony before a House Subcommittee Hearing on Drug Efficacy, Part 2 (91st Cong., 1st Sess., 1969) p. 375, expressed the wish that Congress would "pass" a clarifying amendment on this issue, conceding that the position of his agency was in considerable doubt.

But even if it be assumed that "me-too" drugs are generally entitled to Section 107(c)(4) protection, provided they were generally recognized as safe on October 9, 1962, that does not resolve the right of the plaintiff's "me-toos" to exemption. As has been pointed out, the reasoning on which "me-toos" are regarded as not covered by the

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[19] See, Hagan, *supra*, at p. 125:

> "Furthermore, the concept that new drug clearance by one manufacturer affects the rights of subsequent manufacturers is inconsistent with the established doctrine that new drug clearance is *personal* to the applicant, and does not embrace the drug *per se*."

[20] Cf., comment in Note, *Drug Efficacy and the 1962 Amendments*, 60 Georgetown L. Journal 185, at pp. 206-7 (1971):

> "Ultimately the issue of the status of me-too drugs will have to be squarely faced, and the FDA interpretation of section 107(c)(4), holding that they follow the pioneer's fate, should be repudiated by the courts. In that event the agency will undoubtedly ask Congress for new legislation to remedy the situation. In view of the obvious inequities in the present situation, this would seem to be the most desirable solution."

NDAs granted the manufacturers of their pioneers is that an NDA is regarded as "personal" to the manufacturer submitting the application and to the drug covered. But in this case, the "me-toos" are similar in formula and labeling to other drugs for which the plaintiff itself applied and obtained NDAs. It is true that, in the case of one drug at least, to which reference has already been made, plaintiff's "me-toos" were regarded as exempt, not because plaintiff had an approved NDA for a similar drug, but because FDA was of the opinion that it met the requirements for classification as an old drug. Nonetheless, it is the "personal" character of the NDA that has been deemed as the basis on which it is contended that the "me-toos" are not covered by the NDA granted another manufacturer, albeit the drugs involved may be similar. That reasoning manifestly cannot sustain a right of exemption in favor of plaintiff's "me-toos". The plaintiff's NDAs, being "personal" to it, would cover all its products similar in formula, including those specifically described in its applications and all others like in formula. The similarity in formula, between plaintiff's NDA'd drugs and its "me-toos" is stipulated. Under those circumstances, both the NDA'd and the "me-too" drugs will be treated alike and neither can qualify for exemption under the terms of Section 107(c)(4). It is recognized that this conclusion places the plaintiff in a less favorable position than that occupied by others who may have copied its product prior to October 9, 1962. That inequity is, however, inherent in the law and may only be redressed by Congress, not by the Courts under the guise of construction.

Reversed, with directions to enter judgment for the defendants.

REVERSED.

[Filed May 24, 1972]

APPENDIX B

Judgment

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

No. 71-1596

USV PHARMACEUTICAL CORPORATION, *Appellee,*

v.

ELLIOT L. RICHARDSON, Secretary of Health, Education, and Welfare, Department of Health, Education, and Welfare, and HERBERT L. LEY, JR., Commissioner of Food and Drugs, Food and Drug Administration, *Appellants.*

Appeal from the United States District Court for the Eastern District of Virginia

This cause came on to be heard on the record from the United States District Court for the Eastern District of Virginia, and was argued by counsel.

ON CONSIDERATION WHEREOF, It is now here ordered and adjudged by this Court that the judgment of the said District Court appealed from, in this cause, be, and the same is hereby, reversed.

SAMUEL W. PHILLIPS
Clerk

[Filed July 5, 1972]

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

No. 71-1596

USV PHARMACEUTICAL CORPORATION, *Appellee*,
v.
ELLIOT L. RICHARDSON, ET AL., *Appellants*.

Appeal from the United States District Court for the Eastern District of Virginia, at Alexandria.

Order

Upon consideration of appellee's petition for rehearing and of the suggestion for a rehearing en banc,

IT IS ORDERED, with the concurrence and approval of the panel and in the absence of a request for a poll of the entire court, as provided by Appellate Rule 35(b), that the petition be and it is hereby denied.

DONALD RUSSELL
United States Circuit Judge

APPENDIX D

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
ALEXANDRIA DIVISION

Civil Action No. 4915-A

USV PHARMACEUTICAL CORPORATION, *Plaintiff*

v.

ELLIOT L. RICHARDSON, ETC., ET AL., *Defendants*

Order and Memorandum Opinion

This Court is of the opinion that the plaintiff's bioflavonoids here in question are exempted from the provisions of § 201(p) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 301, et seq., as amended by P.L. 87-781, so long as such products are intended solely for use under conditions prescribed, recommended or suggested in the labeling thereof, as of October 9, 1962, and

IT IS SO ORDERED.

The controversy here turns on whether the plaintiff's bioflavonoids are "new drugs," within the meaning of 21 U.S.C. § 321(p), and thus subject to the efficacy review provisions of the amendment of 1962, or whether they are "old drugs" by reason of the "grandfather clause" in the 1962 amendment—§ 107(c)(4).

The Federal Drug Administration has determined that the plaintiff's bioflavonoids are "new drugs" and has called upon the manufacturer to document and establish their efficacy, as provided for in the 1962 amendment.

Rather than comply, or run the risk of criminal prosecution for non-compliance, the plaintiff brought this suit seeking pre-enforcement relief under 5 U.S.C. §§ 701-704

(Administrative Procedure Act) and 28 U.S.C. § 2201 (Declaratory Judgment Act). That such is proper to resolve conflicts of this type, see *Gardner* v. *Toilet Goods Association*, 387 U.S. 167 (1966).

The "grandfather clause," 107(c)(4) of the Act, reads as follows:

> "In the case of any drug which, on the day immediately preceding the enactment date [October 9, 1962], (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day."

If a statute grants exemptions to certain classes of products from its operation and a dispute arises as to whether or not a given product is entitled to such exemption, it is the Court's function—not the Administrator's—to determine whether or not such product is exempted. Thus, this Court has jurisdiction under the statutes above mentioned to hear and determine this controversy between the parties.

The Court's findings and conclusions follow.

The plaintiff has manufactured and sold its citrus line of bioflavonoid products in interstate commerce in substantial quantities from about 1955 to the present date.

Two of the plaintiff's products were never covered by effective new drug applications. The other seven were all covered at one time. These applications, however, were withdrawn prior to October of 1962. The plaintiff made that clear through its correspondence with the Fed-

eral Drug Administration. It then ceased compliance with the submittal of data and new labeling, as required by the Federal Drug Administration for products covered by effective NDAs.—The record further discloses that the Federal Drug Administration advised the plaintiff in writing that its products covered by NDAs 11474 and 11475 were not new drugs—and it was stipulated that the compound in these two products is identical to the bioflavonoid compound in plaintiff's other products and that the recommended uses of all of the CVP products are essentially the same.

From this evidence, the Court finds that none of the plaintiff's bioflavonoid products in question were covered by an effective NDA as of October 9, 1962.

Whether the plaintiff's bioflavonoids are "new drugs" within the meaning of § 201(p) of the basic Act (codified as 21 U.S.C. § 321 (p)) is the key question for determination here.

> "The term 'new drug' means—
>
> "(1) Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . ."

The word "safe" as used in the basis Act refers to the health of man or animal [1]—efficacy was not added until the 1962 amendment.

Measured by the standard employed by the Federal Drug Administration prior to the effective date of the 1962 amendment, the Court finds that the plaintiff's bioflavonoids were "safe," as that word was then understood.

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[1] 21 U.S.C. § 321(u).

All of the expert witnesses, including those called by the Government, were of the opinion that the plaintiff's bioflavonoids were innocuous when taken by anyone in any condition.

All agreed they were non-toxic and harmless per se in that a normal individual given such a product would not develop an adverse reaction, and were safe for use under the conditions prescribed, recommended or suggested in the labeling—that is, abnormal capillary permeability and fragility—The plaintiff's experts went further—They said the plaintiff's bioflavonoids were not only safe but were quite effective, when used as recommended, in certain types of capillary bleeding.

The Government's experts contend that the safety of a drug can only be determined by its efficacy—a "safe drug" becomes "unsafe" when used in place of the proper drug—the harm comes from the failure to use the best known drug for the treatment of the ailment complained of. This may or may not be so under the 1962 amendment—the Court does not determine that question here.

This decision is limited solely to the determination of whether the plaintiff's drugs are entitled to the exemption set forth in § 107(c)(4) of the Act.

The Clerk will send a copy of this order and memorandum opinion to all counsel of record.

/s/ OREN R. LEWIS
United States District Judge

April 1, 1971

APPENDIX E

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA

Civil Action No. 4915-A

USV PHARMACEUTICAL CORPORATION, *Plaintiff*,

v.

ELLIOT L. RICHARDSON, ET AL., *Defendants*.

Motion for Clarification of Order and Memorandum Opinion

Plaintiff USV Pharmaceutical Corp. respectfully requests the Court's guidance in interpreting the order and memorandum opinion filed herein on April 1, 1971. Specifically, we ask the Court to confirm that in its order and opinion the Court has found:

1. That plaintiff's bioflavonoid products here in question are, today, not "new drugs" under the pre-1962 statutory definition of the term, and therefore exempt from the "new drug" provisions of the statute.

2. That on October 9, 1962 plaintiff's bioflavonoids were, and are today, generally recognized by qualified experts as safe for their intended uses, as the word "safe" was then understood.

Respectfully submitted,

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April 12, 1971

APPENDIX F

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
ALEXANDRIA DIVISION

Civil Action No. 4915-A

USV PHARMACEUTICAL CORPORATION, *Plaintiff*,

v.

ELLIOT L. RICHARDSON, ET AL., *Defendants*.

United States Court House
Tuesday, May 4, 1971
10:00 a.m.

BEFORE: Hon. Oren R. Lewis,
Judge, United States District Court.

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The Court: So that we will get the record clear,—I've got many things to do, and this isn't one of them—on page 4 you have asked me to confirm that I found No. 2 that were and are today generally recognized as safe for their intended uses as the word "safe" was then understood. I believe that I said that when I said that the court finds that these bioflavonoids were safe as that word was then understood.

Mr. Hoffman: That is fine.

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The Court: Now, as your No. 1, you asked me that they are exempt from the new-drug provisions of the statute.

Mr. Hoffman: That is correct, your Honor.

The Court: Well, I couldn't have found that any better in your ways when I made it very clear that that is all I was doing.

Mr. Hoffman: That is right, your Honor.

The Court: I held that this decision, the last paragraph is limited solely to the determination of whether the plaintiff's drugs are entitled to the exemption set forth in the statute; isn't that right? And I held that they were.

Mr. Hoffman: That is right, your Honor.

The Court: Now, I limited it to the exemption.

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The Court: The court clearly intended to hold that they were exempted by the grandfather clause. Now, that is all period.

Mr. Hoffman: Exempted by the grandfather clause from new-drug regulation.

The Court: That is correct, and that is all I held.

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APPENDIX G

UNITED STATES COURT OF APPEALS
FOR THE FOURTH CIRCUIT

No. 71-1243

BENTEX PHARMACEUTICALS, INC., SARON PHARMACAL CORP., MORTON PHARMACEUTICALS, INC., EDWARDS PHARMACAL COMPANY, E. W. HEUN COMPANY, GERIATRIC PHARMACEUTICAL CORP., C. S. RUCKSTUHL COMPANY, WINSTON PHARMACEUTICALS, INC., WABASH PHARMACEUTICALS, INC., SOUTHERN DRUG & MFG. CO., THE BLAINE COMPANY, BROWN PHARMACEUTICAL CO., MAYRAND, INC., PHARMACEUTICAL ASSOCIATES, INC., HALSOM DRUG COMPANY, PISGAH PHARMACEUTICALS, INC., BCR PHARMACAL CO., INC., ALTO PHARMACEUTICALS, INC., PAN-AMERICAN LABORATORIES, INC., PHILLIPS LABORATORIES, INC., PRITCHARD PHARMACEUTICAL PRODUCTS, INC., FOS PHARMACEUTICAL CO., W. E. BOODY & CO., *Appellants*,

v.

ELLIOT P. RICHARDSON, Secretary of the Department of Health, Education and Welfare and CHARLES C. EDWARDS, Commissioner of the Food and Drug Administration, *Appellees*.

Appeal from the United States District Court for the District of South Carolina, at Greenville. Robert W. Hemphill, District Judge.

(Argued December 8, 1971 Decided May 23, 1972.)

Before WINTER, RUSSELL and FIELD, Circuit Judges.

GEORGE F. TOWNES (Sol E. Abrams on brief) for Appellants, and CHARLES R. MCCONACHIE, Attorney, Depart-

ment of Justice, (Will Wilson, Assistant Attorney General, John L. Murphy, Chief, Administrative Regulations Section, William W. Goodrich, Assistant General Counsel, Food, Drugs, and Environmental Health Division, Robert N. Anderson, Attorney, United States Department of Health, Education and Welfare, and Howard S. Epstein, Attorney, Department of Justice, on brief) for Appellees.

RUSSELL, Circuit Judge:

This appeal turns on a construction of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1962.[1] 21 U.S.C. 301, *et seq.* This statute requires pre-marketing approval and clearance of any "new drug" by the Secretary of Health, Education and Welfare.[2] The term "new drug" is defined as one "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective

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[1] There was an earlier Food and Drug Act of 1906. 34 Stat. 768 (1906). It did not provide for any pre-marketing review of the safety of drugs. The sulfanilamide episode in 1938 prompted the enactment of the Federal Food, Drug and Cosmetic Act of that year to replace the earlier Act and to provide, *inter alia*, for such pre-marketing review of "new drugs". See C. W. Dunn, *Federal Food, Drug and Cosmetic Act-A Statement of Its Legislative Record*, pp. 1316-27 (1938). The fears generated by the thalidomide tragedies gave the impetus for the Amendments of 1962. See Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, 185 at p. 191, n. 45 (1971).

[2] Section 355(a), 21 U.S.C.

The actual approval of a "new drug" under the Act is normally processed by the Food and Drug Administration (FDA) in the Department of Health, Education and Welfare (HEW), and the approvals, when granted, are generally referred to as New Drug Approvals (NDAs). FDA, when used herein, refers to the Food and Drug Administration, and NDA is intended to describe an approval by FDA of a "new drug" application under the Act.

for use under the conditions prescribed, recommended, or suggested in the labeling thereof * * *."[3] From a denial of a pre-marketing approval or a withdrawal of a previously given approval, an appeal, originally to the District Court, now to the Circuit Court of Appeals, is authorized.[4] Drugs which do not fit the definition of a "new drug" do not require FDA clearance for marketing. There is no provision in the Act for administrative determination whether a particular drug is a "new drug" nor for any right of appeal from any such determination. The FDA sometimes offers to render "informal advice" as to whether it considers a product a "new drug" but it uniformly designates such opinion "advice."[5] Accordingly, the responsibility for determining whether its product is a "new drug," requiring pre-marketing clearance by FDA, rests on the manufacturer, who must act at its peril.[6] If it makes an incorrect determination and seeks to market without FDA clearance a drug meeting the definition of a "new drug," it lays itself open to drastic judicial procedures that may be invoked by FDA, i.e.: The product may be seized in an *in rem* action instituted by the Government;[7] its sale may

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[3] Section 321 (p)(1), 21 U.S.C.

See, also, *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C.Md. 1967) 274 F.Supp. 443, 445, n. 2:

> "The statutory definition of the phrase 'new drug' controls this case, regardless of any other meaning attributable to the phrase or to the word 'new' by common understanding or other authority."

[4] Section 355(h), 21 U.S.C.

[5] 21 C.F.R. 130.39.

[6] Cf. *United States* v. *Dotterweich* (1943) 320 U.S. 277, 281, where, speaking of the Act of 1938, the Court said:

> "In the interest of the larger good it puts the burden of acting at hazard upon a person otherwise innocent but standing in responsible relation to a public danger."

[7] Section 334, 21 U.S.C.

be enjoined in an action begun by the Government;[8] in addition, the manufacturer may be subjected to criminal action.[9] All these remedies must be prosecuted in the District Court and the role of the Secretary is that of plaintiff or prosecutor. The Act thus establishes two forums for the regulation of drugs: One is administrative and deals with the procedures for securing pre-marketing clearances for the statutorily defined "new drug," with right of appeal from a denial of approval, or withdrawal of a previous approval, to the District Court, later changed to the Court of Appeals; the other is judicial and is intended to make effective and give strength to the requirement that "new drugs" be cleared as safe before marketing by providing the Government with certain potent judicial remedies, *available exclusively in the District Court.*

Under the 1938 Act, a new drug was one "not generally recognized by experts * * * as safe for its intended use." The Amendments added "effectiveness" as well as "safety" to the definition. Simply stated, the change effected by the Amendments was that, whereas prior to the 1962 Amendments a drug which was generally recognized as safe was not a "new drug," the Amendments defined a drug as "new" if it were not generally recognized as both safe *and effective.* Furthermore, they replaced the provision for automatic approvals of applications not disapproved within a fixed time with a requirement of a positive act of approval on the part of FDA.[10] They proceeded to provide that the Secretary must find as a basis for clearance of a new drug not only safety but "substantial evidence" of effectiveness, "consisting of adequate and well-controlled investigations, including clinical investigations, by experts

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[8] Section 332, 21 U.S.C.

[9] Section 333, 21 U.S.C.

[10] Section 355(e), 21 U.S.C.

qualified by scientific training and experience to evaluate the effectiveness of the drug involved." The applicability of these amendments, including the revised definition of "new drug" to drugs already marketed, either under previously issued NDAs, or as "old drugs" requiring no FDA approval, was carefully spelt out in the Amendments and certain "grandfather rights" were granted. For all previously NDA'd drugs, the Amendments conferred a grace period of two years after the effective date of the Amendments within which to prepare evidence to satisfy the new requirement of efficacy added by the revised definition of "new drug"; during that "transitional" period no revocation or withdrawal of approval because of a lack of substantial evidence of efficacy of such drugs was permitted.[11] For a drug, however, which on the day prior to the enactment of the Amendments was (1) being "commercially used or sold in the United States," (2) "was not a new drug as defined by" the pre-Amendment statute and (3) "was not covered by an effective (new drug) application, • • •" "on the day immediately preceding the enactment date" of the Amendments, there was a permanent exemption from the efficacy provisions of the Amendments so long as the drug's labeling remained the same.[12] In summary, these provisions required that, "Those drugs which had obtained effective NDAs must be proven efficacious after two years; those which had not need never be proven

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[11] Section 107(c)(3), P.L. 87-781, Section 321, Supplement 1972, 21 U.S.C.

[12] Section 107(3)(4), P.L. 87-781, Section 321, 1972 Supplement, 21 U.S.C.; see, also, *Tyler Pharmacal Distrib. Inc.* v. *U. S. Dept. of Health, E. & W.* (7th Cir. 1969) 408 F.2d 95, 99.

It should be noted that Section 321(p)(1) provides a "grandfather clause" applicable to pre-1938 drugs. This clause is not relevant to this action, which is concerned with drugs introduced between 1938 and 1962, and the subsequent references to "grandfather clause" in this opinion are to section 107(c)(4).

efficacious so long as they had become safe prior to the 1962 Amendments." [18]

The "grandfather clause" set forth in Section 107(c)(4) simply continues for the products satisfying its criteria the pre-1962 definition of a "new drug." Its effect is to assure that a drug which was generally recognized by qualified experts as safe for the purposes recommended for its use on October 9, 1962, need not be NDA'd as *effective* under the new requirements for the issuance of an NDA as a "new drug." But any drug, whether requiring an NDA or not, whether a "new drug" or an "old drug," is subject to the misbranding provisions of the Act and may be proceeded against on that basis. A false claim of either safety or effectiveness constitutes misbranding, rendering a drug subject to both civil and criminal penalties. *United States* v. *Article of Drug Labeled Decholin* (D.C.Mich. 1967) 264 F. Supp. 473, 482-3; *United States* v. *Lanpar*

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[18] Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 Georgetown Law Journal, p. 196 (1971).

See, also, *United States* v. *Allan Drug Corp.* (10th Cir. 1966) 357 F.2d 712, 719, note 9, quoting from the Supplemental Report of the Senate Committee on Drug Amendments of 1962, as set forth in the notes to Section 321, 21 U.S.C.:

> "Thirdly, in the case of a drug on the market which was never subject to the new-drug procedure before, the amendments to the new definition relating to drug effectiveness would not apply to existing labeling claims."

In the Conference Report of the House Managers on the Amendments, it was stated that the Amendments included "the Senate language providing with respect to existing label claims of drugs that have never previously been subject to the new-drug procedure substantially the same savings provisions as the corresponding provision of the House bill (Section 197(d))." *U.S. Code Congressional and Administrative News*, 87th Congress, 2d Session (1962), p. 2932. Again, in H. R. Rep. #2526, p. 23, it is stated that the exemption granted by the "grandfather clause" applies "to existing claims of drugs that have never been subject to the new-drug procedure".

Company (D.C.Tex. 1968) 293 F. Supp. 147, 153-4.[14] Accordingly, in *United States* v. *Guardian Chemical Corporation* (2d Cir. 1969) 410 F.2d 157, a drug manufacturer was acquitted of a charge of marketing a "new drug" without an NDA, but was convicted under a separate count of the indictment charging misbranding. "Thus," as one commentator has aptly stated, "the amplications of the FDA's authority (as granted by the 1962 Amendments) is (was) not due to the absence of power to proceed against ineffective drugs, but rather to authorize the exercise of that power at the initial stage, that is, *before* marketing, and also to shift the burden of proof to the applicant." Jurow, *The Effect on the Pharmaceutical Industry of the "Effectiveness" Provisions of the 1962 Drug Amendments*, 19 Food, Drug, Cosmetic Law Journal, 110, at p. 116 (1964).[15]

The plaintiffs, manufacturers of a prescription drug containing pentylenetetrazol and nicotinic acid, claim the

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[14] See, also *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F.2d 536, 548:

> "A good case could certainly be made that quite apart from this, the 'efficacy' of a drug is necessarily related to the use recommended."

[15] See, also Senate Report #1744, *U.S. Code Congressional and Administrative News*, 87th Cong., 2d Sess. (1962), pp. 2892 and 2893, where, in justifying the Amendments, it is stated:

> "* * * where a drug is essentially innocuous, it (FDA) must clear the drug despite the fact that its claim of effectiveness is not borne out by the evidence. In such cases the Food and Drug Administration may proceed against the drug manufacturer by seizure of the drug for misbranding. However, the Department believes that the manufacturer should satisfy the Food and Drug Administration that his product is effective for the purposes claimed before it is marketed. * * * No question of safety is involved, and the Food and Drug Administration presently has ample power, including seizure, to proceed against any safe drug for which unsupported claims of effectiveness are made."

protection of the "grandfather clause" included in Section 107(c)(4) for their products and that contention represents the substantive issue in this case. It is undisputed that plaintiffs had marketed their product commercially for many years prior to and on October 9, 1962,[16] without an NDA under the claim that it was not a "new drug" within the definition of the Act, and therefore required no NDA. Such claim was supported, it is asserted, both by previous informal advice of the Secretary and by the general recognition of the safety of such product by "experts qualified by scientific training and experience" to make such evaluation. The defendants, the Secretary of HEW and the Commissioner of Food and Drugs, in their brief, concede that "Over the years since 1938" and until 1968, the Food and Drug Administration had given the opinion that certain pentylenetetrazol combinations similar to those of the appellant were not "new drugs."[17] Moreover, the District Court observed in its opinion that there was "no contention (by the FDA) that the use of the plaintiffs' drugs in treatment of the symptoms of senility in geriatric patients is in any way harmful to them, either directly or indirectly by causing the disuse of better drugs." On this basis, the plaintiffs contended that they met exactly the criteria established for exemption from the requirements of general recognition by qualified experts of the effective-

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[16] This was the day "immediately preceding the enactment date" of the Amendments of 1962.

[17] It is, of course, axiomatic that such opinions or advice can create no estoppel against the Government. *AMP, Incorporated* v. *Gardner* (D.C.N.Y. 1967) 275 F.Supp. 410, 412, n. 1, aff. 389 F.2d 825, cert. den. 393 U.S. 825, reh. den. 395 U.S. 917. The most that can be claimed for such opinions is that they lend color and good faith to the plaintiffs' claims. FDA not only has the right but is obligated to change its opinion if it learns its prior position was erroneous. *United States* v. *60 28-Capsule Bottles, More or Less, etc.* (D.C.N.J. 1962) 211 F.Supp. 207, 215, aff. 325 F.2d 513.

ness of their products as provided in the permanent grandfather section of the 1962 Amendments.

Prior to the filing of this action, however, the defendants withdrew their advice that products such as those distributed by the plaintiffs were "old drugs" and contended that such products did not qualify for exemption under the "grandfather clause," Section 107(c)(4). The basis for this contention was the claim (1) that these drugs were not generally recognized by qualified experts as safe as of the effective date of the Amendments of 1962 and (2) that they were "me-too" drugs, whose marketability without FDA clearance depended in turn on the NDAs granted the basic drug, and for that reason must be regarded as drugs covered by an effective NDA on the effective date of the Amendments.[18] Faced with this threat, the plaintiffs began

[18] The defendants assert that three "new drug" applications filed by other manufacturers and earlier approved by the FDA covered drugs similar in every particular to those marketed by the plaintiffs. Proceedings for withdrawal of the approval of such "new drugs" had been begun by FDA in advance of the filing of this action. In fact, such proceedings to a large extent prompted this action. It is the contention of the defendants that the withdrawal of what they describe as "the primary NDAs" operates to remove the marketability from what they assert are the "me-toos" or non-NDA'd drugs which are similar to other drugs which have secured effective NDAs. The plaintiffs deny that their drugs are like those previously NDA'd. They argue that those NDA'd products, unlike theirs, are intravenously administered or are a compound containing, in addition to the components of plaintiffs' drugs, reserpine. Such changes in formula or method of administering vitiated any claim by their manufacturers that they were marketing an old drug and required an approval as a new drug. The plaintiffs assert their drugs are not subject to any such disability. These, however, are questions of fact not relevant to the simple question of jurisdiction presented by this appeal and may be inquired into on remand. Even if the products of the plaintiffs be deemed "me-too" drugs (i.e., simply "a copy of a pioneer drug which preceded it on the market"), it is by no means clear that they do not "meet the requirements for section 107(c)(4) protection" and the argument of the Government to the con-

this action for a declaratory judgment sustaining their right to exemption from proof of the effectiveness of their product and for injunctive relief awaiting the disposition of their claim for exemption. The defendants directed against the complaint a motion to dismiss or for summary judgment, which, in essence, (1) asserted primary jurisdiction in the Secretary to determine whether the products of the plaintiffs met the requirements for exemption under Section 107(c)(4), particularly whether they were "new drugs," requiring pre-marketing approval under the Act, (2) denied the propriety of a declaratory judgment action, and (3) claimed that the products of the plaintiffs were "new drugs" which did not qualify for exemption under the "grandfather clause."

The District Court sustained the right of the plaintiffs to maintain a suit for a declaratory judgment and the jurisdiction of the Court in such action to determine judicially whether the products of the plaintiffs were "new drugs," on the effective date of the Amendments, and whether they were or were not entitled to the benefits of the "grandfather clause."[19] However,—and this is the nub of the controversy

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trary has been described as "lacking in merit." See, Note, *Drug Efficacy and the 1962 Amendments,* 60 Georgetown Law Journal, 185 at p. 203-207 (1971); Hagan, *Grandfather Protection under the Drug Amendments of 1962,* 19 Food Drug Cosmetic Law Journal 119, at p. 125 (1964).

[19] In support of the right of the plaintiffs to maintain a suit for declaratory judgment, the District Court relied on *Abbott Laboratories* v. *Gardner* (1967) 387 U.S. 136 and the companion case of *Toilet Goods Assn.* v. *Gardner* (1967) 387 U.S. 158. Additional support for such right is found in *AMP, Incorporated* v. *Gardner, supra; Durovic* v. *Richardson* (D.C. Ill. 1971) 327 F.Supp. 386; *Lemmon Pharmacal Co.* v. *Richardson* (D.C. Pa. 1970) 319 F.Supp. 375. The right of the Court to determine the applicability of the "grandfather clause" is equally clear and has been sustained in *United States* v. *Articles of Drug Labeled "Quick-O-Ver"* (D.C. Md. 1967) 274 F.Supp. 443, 445; and *United States* v. *Article Consisting of 36 Boxes, etc.* (D.C. Del. 1968) 284 F.Supp. 107, 112, n. 13, aff. 415 F.2d 369.

between the parties on this appeal—it concluded that the Secretary had concurrent jurisdiction to determine whether plaintiffs' products were "new drugs," requiring pre-marketing clearance, and that, because of the greater expertise of the Secretary in the field, it deferred to the Secretary's assumed jurisdiction to determine whether the drugs of the plaintiffs came within the exemption provided by the "grandfather clause." It enjoined any action against the plaintiffs and their products until the plaintiffs had been accorded a hearing before the Secretary on the issue of the qualifications of these drugs for protection under the "grandfather clause." It is the conclusion of concurrent jurisdiction in the Secretary and deference to that assumed concurrent jurisdiction from which the plaintiffs have prosecuted this appeal.

The defendants, on the other hand, have not cross-appealed and have accordingly acquiesced in the decision of the District Court that the action is properly maintainable as a declaratory judgment proceeding under Section 2201, 28 U.S.C. and that the District Court has jurisdiction over the substantive issue in this case, i.e., whether plaintiffs' products are "new drugs," as defined in the Act. The question in the case is thus whether the Secretary has concurrent jurisdiction to determine whether a drug is a "new drug" under the Act or whether that issue is cognizable only in the District Court. Contrary to the conclusion of the District Court, we conclude that the Act confers no such jurisdiction on the Secretary and, therefore, no basis for any deference by that Court to the concurrent jurisdiction of the Secretary.

The FDA has neither primary jurisdiction, as the defendants argue, nor concurrent jurisdiction, as the District Court concluded, to adjudicate whether a product is an old or a new drug. It may, in its prosecutorial role, reach a conclusion that a product being marketed is a "new drug" requiring pre-marketing approval; but that opinion is not adjudicatory, it is only the basis on which the FDA, as the

prosecutor or initiator of either a seizure or injunctive action in the District Court, may invoke the jurisdiction of that Court to determine, among other issues, whether the drug challenged is a "new drug." There is manifestly no provision in the Act for an administrative proceeding before the Secretary to compel the filing of a "new drug" application or to halt the marketing of a drug for which there is no approval by the Secretary. It is not without significance that, so far as the official reports reflect, the Secretary has never attempted directly to exercise such jurisdiction. The only occasions on which he has sought to assert such jurisdiction has been as an element in his defense to a declaratory judgment action.[20] Moreover, when FDA undertook its new responsibilities under the 1962 Amendments, it sought merely to review "the efficacy of *all new drugs that had been cleared*, for safety only, between 1938 and October 10, 1962" (Italics added) and enlisted the services of the National Academy of Sciences—National Research Council for this limited task. It did not assert the right to review, or assume the burden of reviewing, for efficacy, drugs such as those involved here, which had been commercially marketed on the basis of a general recognition of safety without an effective NDA as of the effective date of the 1962 Amendments. It, thus, recognized that its adjudicatory rights extended merely to the approval, or the withdrawal of approval,[22] of a drug embraced in a "new drug" application that had been ap-

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[20] See, *Hynson, Westcott & Dunning, Inc.* v. *Richardson* (Civ. No. 21112, D. Md., decided 9/16/70); and *Ciba Corp.* v. *Richardson* (Civ. No. 1210-70, D. N.J., decided 3/10/71); but cf., *Lemmon Pharmacal, supra.*

[21] See *Pfizer, Inc.* v. *Richardson* (2d Cir. 1970) 434 F.2d 536, 539, and 31 F.R. 9426.

[22] The authority of the Secretary to withdraw an approval of any "new drug" application filed under the Act of 1938 after hearing is specifically granted by Section 355(e), 21 U.S.C.

proved. This confirms the conclusion that the halting of the marketing of a drug, for which there is no NDA, may not be by administrative action but must be by an injunction or *in rem* seizure proceeding, in which the Secretary appears, not in a judicial but in a prosecutorial role.[23] Those are the procedures prescribed and available to the Government under the Act.[24] The Secretary, it is true, has offered to provide "advice" on whether a product meets the qualification of an old drug but he categorizes his action in such instances as merely "advice" and makes no claim of finality therefor. Nor is there, as we have already observed, any provision for judicial review of such "advice."[25] The only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of an approval, of a "new drug" application.[26] That this is so follows from the limitations placed by the Act on judicial review of the decisions of the Secretary. The Secretary himself asserted, shortly after the enactment of the 1962 Amendments, in *Turkel* v. *Food and Drug Administration, Dept. of H.E.W., supra,* at p. 845, that the Act "grants a

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[23] Of course, in a proper case the Government may also institute criminal proceedings in the District Court. See Section 333, 21 U.S.C.

[24] Cf. *United States* v. *Allan Drug Corporation* (10th Cir. 1966) 357 F.2d 713, 718, cert. den. 385 U.S. 899, in which the Secretary is quoted to the effect that, " 'As to drugs already on the market that have never been subject to the new-drug procedure but are not generally recognized as effective, the burden remains on the Government to prove *in court,* insofar as unchanged labeling claims are concerned, they do not have their claimed effect. If the labeling claims are changed, however, these must be approved under the new-drug procedure.' " (Italics added.)

[25] See *Turkel* v. *Food and Drug Administration, Dept. of H.E.W* (6th Cir. 1964) 334 F.2d 844, 846, cert. denied 379 U.S. 990, rehearing denied 380 U.S. 927: "The jurisdiction of the United States Courts of Appeal to review administrative acts of federal agencies is wholly dependent upon statute."

[26] Section 355(b), 21 U.S.C.

right to appeal only from an order of the Food and Drug Administration approving or disapproving a New Drug Application." In keeping with the Secretary's contention as to the extent of his adjudicatory powers, the Court in that case held that the right of appeal from an order of the Secretary "applies only to an order of the Secretary refusing or withdrawing approval of an application for sale and distribution of a new drug" (at pp. 845-6). It is not to be assumed that the Act confers an adjudicatory right on the Secretary from which no judicial review, however limited, is provided or allowed. Yet this is the unusual situation that would be presented if the Secretary were held to have jurisdiction to adjudicate whether a drug meets the statutory criteria of a "new drug."[27]

The District Court, in finding concurrent jurisdiction, held that "This grant of authority to approve or withhold approval of new drug application, * * * necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which required an approved new drug application for lawful interstate shipment." This reasoning assumes that an application for approval by the Secretary under the Act poses as its initial issue whether the product is a new drug. No such issue is posed by the application. The very filing of the application is a concession and recognition by the applicant-manufacturer that the article is a "new drug"; otherwise, there would be no reason to file the application. As a matter of fact, in the prescribed form of application, the applicant describes his product as "new drug." 21 C.F.R. 130.4. The applicant makes the determination whether his product is a "new drug" and whether he must file for pre-marketing clearance by the Secretary. And when filed, the application puts in issue only one question: Is the article safe and effective? That and that alone is the issue to be

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[27] Cf. *Abbott Laboratories* v. *Gardner* (1967) 387 U.S. 136, at p. 140.

considered by the Secretary in connection with an application for approval filed by a manufacturer under Section 355(d), 21 U.S.C. That issue is quite different from that presented when there is an issue whether a drug fits the statutory definition of "new drug" in the Act. The criterion for ascertaining whether a product is within the statutory definition of "new drug" under the Act is not safety and effectiveness *per se*, which, as we have observed, is the issue before the Secretary in connection with application for approval of a "new drug," but "whether the government has shown by a preponderance of the evidence that the 'drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof.' "[28] That is an issue that must be and is resolved, sometimes with, and at other times without a jury, in practically every injunctive, seizure, or criminal proceeding under the Act. See, for instance, *United States* v. *Articles of Drug Labeled "Quick-O-Ver," supra*; *United*

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[28] *United States* v. *Articles of Drug Labeled "Quick-O-Ver", supra*, at pp. 445-6.

See, also:

AMP, Incorporated v. *Gardner, supra*, at p.831:

"But the safety of the products is not what is at issue here. The question is whether there is general recognition among qualified experts of the products' safety and effectiveness—if there is not, the products must be submitted to the Secretary of Health, Education and Welfare for a determination as to safety, adequacy of testing, etc."

United States v. *Article of Drug, etc.* (5th Cir. 1969) 415 F.2d 390, 392:

"Both sides agree that the nature of expert opinion about Furestrol, and not its actual safety or effectiveness, is the ultimate fact issue."

Cf., *United States* v. *Seven Cartons, More or Less, etc.* (7th Cir. 1970) 424 F.2d 1364, 1365.

States v. *41 Cases, More or Less* (5th Cir. 1970) 420 F.2d 1126, 1128; *United States* v. *Article of Drug, etc., supra,* at p. 392; *United States* v. *Article . . . Consist. of 216 Carton* (2d Cir. 1969) 409 F.2d 734, 742; *United States* v. *Article Consisting of 36 Boxes, etc., supra,* at p. 113; see, also, *United States* v. *Article of Drug, etc.,* (D.C.Md. 1971) 331 F. Supp. 912, 915-7. That was one of the issues resolved in the declaratory action of *Lemmon Pharmacal Co.* v. *Richardson, supra.*[29] It is manifestly a justiciable issue and the plaintiffs are entitled to a judgment on that issue by the Court, which alone has the jurisdiction to resolve it. In the absence of any statutory review proceedings within which they may assert their claim of exemption, the plaintiffs are not to be compelled to proceed at their peril, subject to the possibility of both civil and criminal penalties, but are entitled to seek relief by way of a declaratory judgment action. The District Court should accordingly have retained jurisdiction and proceeded to determine whether the plaintiffs' drugs met the criteria for exemption under Section 107(c)(4). We deem it premature for us to consider at this stage whether plaintiffs' products meet such criteria. That issue was not developed in the record before, or ruled on by, the District Court.[30] Upon remand, the issue can be considered by the Court in the light of the record that may be made by the parties.

REMANDED, WITH DIRECTIONS.

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[29] In discussing this case, the commentator in 60 Georgetown Law Journal, p. 199, note 87, says:

> "In *Lemmon Pharmacal,* the Court, while noting that determining safety and efficacy would normally be within the primary jurisdiction of the agency, concluded that the question of section 107(c)(4) protection was properly before it."

[30] See *United States* v. *Article Consisting of 36 Boxes etc., supra,* at p. 113.

APPENDIX H

Notice: This opinion is subject to formal revision before publication in the Federal Reporter or U.S.App.D.C. Reports. Users are requested to notify the Clerk of any formal errors in order that corrections may be made before the bound volumes go to press.

UNITED STATES COURT OF APPEALS
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 24,900

USV PHARMACEUTICAL CORPORATION, *Petitioner*

v.

SECRETARY OF HEALTH, EDUCATION & WELFARE and COMMISSIONER OF FOOD & DRUGS, *Respondents*

Petition for Review of an Order of the Commissioner of Food & Drugs

---

Decided August 14, 1972

Mr. Joel E. Hoffman, with whom *Messrs. Robert L. Wald*, *Stephen M. Truitt* and *Miss Selma M. Levine* were on the brief, for petitioner.

Mr. Howard S. Epstein, Attorney, Department of Justice, with whom *Messrs. John L. Murphy*, Chief, Administrative Regulations Section, Department of Justice, *William W. Goodrich*, Assistant General Counsel, and *Joanne S. Sisk*, Attorney, Department of Health, Education and Welfare, were on the brief, for respondent.

Before ROBINSON, ROBB and WILKEY, *Circuit Judges*.

ROBB, *Circuit Judge:* The petitioner, USV Pharmaceutical Corporation (USV), is engaged in the manufacture and marketing of a line of citrus bioflavonoid drugs known as

CVP.[1] The petitioner challenges an order of the Commissioner of Food and Drugs [2] withdrawing approval of three New Drug Applications held by USV for these drugs. The order was issued pursuant to section 505(e) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 355(e) (1970), and its effect is to make the interstate distribution of the drug illegal. 21 U.S.C. §§ 331, 355. The Commissioner says that his order is supported by his finding that there is a lack of substantial evidence, as that term is defined in the Act, 21 U.S.C. § 355(d), that the drugs will have the effectiveness claimed for them. The petitioner counters that the order is invalid because of substantial defects in the proceedings upon which it is based. Reviewing the matter pursuant to 21 U.S.C. § 355(h), we are constrained to agree with the petitioner.

Under the statutory scheme the Commissioner approves or disapproves a drug upon the basis of what is known as a New Drug Application (NDA) submitted by the person proposing to introduce the drug into interstate commerce. In 1956 and 1957 three NDAs for the petitioner's CVP drugs were approved by the Commissioner pursuant to the Federal Food, Drug and Cosmetic Act of 1938, 52 Stat. 1041, 1052, 21 U.S.C.A. §§ 321(p), 355 (1961). Under this statute drug approval was granted if the sponsor submitted proof establishing that the drug was safe for its intended use. No determination of the drug's effectiveness for its

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[1] CVP is the trade name under which the petitioner markets drugs containing citrus flavonoid compound, a derivative of citrus fruit pulp and peel, and vitamin C, with and without vitamin K. CVP is a bioflavonoid, a generic term which may refer not only to citrus flavonoid compounds but also to any of its separate components. These drugs are recommended by the petitioner for the control of abnormal capillary premeability and a number of serious blood disorders.

[2] The Commissioner acted under authority delegated by the Secretary of Health, Education and Welfare. 21 C.F.R. § 2.120 (1971).

prescribed uses was required. In 1962, however, the relevant sections of the statute were amended to require a showing by a drug sponsor that a drug was both safe and effective for its prescribed uses. Act of October 10, 1962, 76 Stat. 781-783, 784, 785, 21 U.S.C. § 355. Among other things the new Act provided that:

> The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds * * * (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof. . . . Any order under this subsection shall state the findings upon which it is based. 21 U.S.C. § 355(e).

The Act defined the term "substantial evidence" as follows:

> As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. 21 U.S.C. § 355(d).

The proceedings to withdraw approval of the petitioner's CVP drug applications were under 21 U.S.C. § 355(e).

By notice in the Federal Register on July 9, 1966 the Commissioner announced that the National Academy of Sciences—National Research Council (NAS-NRC) had "agreed to assist the Food and Drug Administration in its review of the claims of effectiveness for drugs cleared through the new-drug procedures from 1938 until October 10, 1962." 31 Fed. Reg. 9426. The notice directed holders of such approved new-drug applications to submit certain specified data and material to NAS-NRC, in order to

> facilitate this review and a determination of whether there may be ground for invoking section 505(e) of the Federal Food, Drug, and Cosmetic Act, and to provide each holder of such an approved new-drug application an opportunity to present for the consideration of the reviewing experts the best data available to support the medical claims. . . .

Among the materials to be submitted were:

> f. Current labels and package inserts (attach 10 copies of each to original of form; 1 copy of each to duplicate).
>
> g. List of literature references most pertinent to an evaluation of the effectiveness of the drug for the purposes for which it is offered in the label, package insert, or brochure. Approximately 5 to 10 key references, if available (attach 10 copies of the list to original of form and 1 copy to duplicate).
>
> h. Unpublished articles or other data pertinent to an evaluation of the claims (one copy only; attach to duplicate).

Responding to the Commissioner's notice of July 9, 1966 USV submitted two bibliographies, one containing nine references, the other sixteen. This submission was reviewed by two NAS-NRC panels which in due course reported to

the Commissioner. The complete report of the Panel on Drugs Used in Hematologic Disorders was as follows:

C.V.P. with VITAMIN K
NDA 9965
LOG 734

Panel on Drugs Used in Hematologic Disorders

INDICATIONS

I. As a supplementary source of bioflavonoids, ascorbic acid, and menadione.
EVALUATION: Ineffective.
COMMENTS: The label correctly states that the dietary need for these agents has not been established, in agreement with Burns.

DOCUMENTATION:

1. Burns, J. J. Water-soluble vitamins; II. ascorbic acid (vitamin C), pp. 1673-1680. In L. S. Goodman and A. Gilman, Eds. The Pharmacological Basis of Therapeutics. (3rd ed.) New York: The MacMillan Co., 1965.

Approved by William [illegible]
Chairman

So far as material the report of the Panel on Drugs Used in Metabolic Disorders was as follows:

DUO-C.V.P.
NDA 9965
LOG 733

Panel on Drugs Used in Metabolic Disorders

INDICATIONS

None.

GENERAL COMMENTS

I. There is no package insert, but just a label indicating that this is a "supplementary source of bioflavonoids and ascorbic acid." There is no

definite claim for therapeutic use and a statement on the label admits that "the need for bioflavonoids in human nutrition has not been established." However, the inference is that there is indeed a need for such a product. The references support this inference, in that everything from threatened abortion to bleeding gums is reported to have responded. The use of these materials as hemostatic agents for capillary fragility is felt to be unjustifiable and not proved. The Panel recommends that there should be a clear statement as to the use of this preparation.

II. The Panel finds that the term "minimum daily adult" requirement is meaningless because variations in nutritional needs depend on the health, sex, age, and physical activity of the individual. The term "dietary allowances" is preferred.

III. See the general statement on multiple-vitamin preparations.

Approved by D. H. Nelson
Chairman

On January 23, 1968 the Commissioner announced that the Food and Drug Administration, having received the NAS-NRC report, "has considered the report and has concluded on the basis of the report and its own evaluations that there is no evidence that * * * bioflavonoids are effective for use in man for any condition." 33 Fed. Reg. 818. The Commissioner noted that lack of substantial evidence of effectiveness of a drug was a basis for withdrawing approval of a new-drug application, and that the Commissioner intended "to publish a notice of opportunity for a hearing on a proposal to withdraw approval" of new-drug applications for the bioflavonoids. The Commissioner stated, however, that before taking such action he invited all interested holders of new-drug applications to attend

a meeting on January 31, 1968 "to discuss the procedural matters involved in the proposed action * * * and to attempt to identify and resolve problems that may be anticipated as a result of the actions to be taken." The meeting was held on January 31, 1968 at which time the Food and Drug Administration again invited the submission of additional scientific and medical information that might be pertinent to the question of the effectiveness of the drugs. In response, USV submitted certain additional information in the form of reports and reprints.

By notice published in the Federal Register on July 10, 1968, 33 Fed. Reg. 9908, the Commissioner announced that "[t]he additional information received, considered together with other information available, did not provide substantial evidence of effectiveness of such drugs for use in man for any condition." Accordingly, the Commissioner gave notice that he proposed to withdraw approval on the ground that there was a lack of substantial evidence that any bioflavonoids had the effect which the drugs purported or were represented to have under the conditions for use prescribed, recommended or suggested in the labeling thereof, or that such articles alone, or as added components with other drugs, were effective for use in man in any condition. Continuing, the notice stated that "the Commissioner will give each applicant and any interested person who would be adversely affected by an order withdrawing such approval an opportunity for a hearing at which time such persons may produce evidence and arguments to show why approval of any new-drug application listed herein should not be withdrawn." 33 Fed. Reg. 9909.

On August 6, 1968 the petitioner filed an action in the United States District Court for the Eastern District of Virginia seeking a declaratory judgment that none of its products named in the Commissioner's notice was a new drug within the meaning of the Federal Food, Drug and Cosmetic Act, as amended. *USV Pharmaceutical Corp.* v.

Richardson, Civ. No. 4915-A (E.D. Va.).[3] On the following day, August 7, the petitioner requested the Commission to stay all further proceedings under the Commissioner's notice of July 10, 1968, pending the disposition of the declaratory judgment action. In addition to this request the petitioner on August 9, 1968 requested a hearing before the Commissioner on his proposal to withdraw approval of the petitioner's new-drug applications. On August 16 the Commissioner refused to stay the proceedings, stating:

> The National Academy of Sciences-National Research Council reported that there is no evidence that bioflavonoids are effective for use in man for any condition. This proceeding was initiated to provide an opportunity, to all interested parties, for a hearing on the proposal. This proceeding will afford you both an administrative hearing and an opportunity for judicial review if withdrawal of the new drug applications follow [*sic*].

The regulations in force in 1968 provided that upon timely request for a hearing "a hearing examiner will be named and he shall issue a written notice of the time and place at which the hearing shall commence. . . ." The date of the hearing was required to be not more than 120 days after the date of the Commissioner's notice of proposed withdrawal of approval "unless the hearing examiner and the applicant otherwise agree." 21 C.F.R. § 130.14 (1968). The Commissioner, however, did not name a hearing examiner and no further action was taken in the administrative proceedings until 1970.

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[3] After a hearing the District Court held, on April 1, 1971, that USV's bioflavonoid products were not "new drugs" within the statutory definition. On May 24, 1972 the Circuit Court of Appeals for the Fourth Circuit reversed, rejected the claim for exemption, and directed the district court to enter judgment for the defendants. *USV Pharmaceutical Corp.* v. *Richardson*, No. 71-1596 (4th Cir., May 24, 1972).

On May 8, 1970 the Commissioner revised the regulations governing hearings in NDA revocation proceedings. The revised regulations provide that a request for a hearing must state the reason why an NDA should not be withdrawn, "together with a well-organized and full-factual analysis of the clinical and other investigational data [the applicant] is prepared to prove" and setting forth "specific facts showing that there is a genuine and substantial issue of fact that requires a hearing." The regulations further provide that:

> When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data. 35 Fed. Reg. 7252 (1970); 21 C.F.R. § 130.14(b).

On July 7, 1970 the Commissioner wrote to the petitioner referring to the Commissioner's notice of proposed withdrawal published July 10, 1968 (33 Fed. Reg. 9908), the petitioner's request for a hearing dated August 9, 1968, and the revised regulations of May 8, 1970. The letter continued:

> The May 8 regulations are applicable to any request for a hearing. You should amend your request for a hearing to comply with those regulations, i.e., by submitting a well-organized and full-factual analysis of the clinical and other investigational data you are prepared to prove in a hearing, setting forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing.

Replying to the Commissioner's letter of July 7, the petitioner by letter dated August 7 requested a stay of all further proceedings before the Commissioner because (1) the petitioner's action for declaratory judgment in the Eastern District of Virginia, in which the petitioner asserted that its drugs were not "new drugs", was scheduled for trial on October 23, 1970, and (2) the validity of the revised regulations of May 8 was under challenge in the United States District Court for the District of Delaware.[4] In conclusion, USV requested "that if a stay is denied the company be given at least thirty days from receipt of notice of the denial to file a further response to your letters of July 7."

On October 14, 1970 the Commissioner replied to the petitioner's letter of August 7. The Commissioner noted that his letter of July 7 "suggested the request for a hearing be amended within 30 days from receipt of that letter" but that no amendment had been received.

> Accordingly, [said the Commissioner,] we conclude that no useful purpose will be served by further delaying the processing of a final order to withdraw approval of the subject new drug applications. The pending litigation in the United States District Court for the Eastern District of Virginia and the United States District Court for the District of Delaware do not provide sufficient ground to further delay these proceedings.
>
> Your request for a 30-day extension, in the event of our denial of a stay, is also denied.

---

[4] The Commissioner's regulations and standards were challenged by other litigants in the federal courts. *See Upjohn Co.* v. *Finch*, 422 F.2d 944 (6th Cir. 1970); *Pharmaceutical Manufacturers Ass'n* v. *Finch*, 307 F. Supp. 858 (D. Del. 1970); *Pharmaceutical Manufacturers Ass'n* v. *Richardson*, 318 F. Supp. 301 (D. Del. 1970). The challenges were unsuccessful.

On October 15, 1970 the Commissioner issued an order withdrawing the petitioner's NDAs. The ground of the order was stated to be that the Commissioner:

> finds that on the basis of new information before him with respect to each of said drugs, evaluated together with the evidence available to him when each application was approved, there is a lack of substantial evidence that each of the drugs will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof. 35 Fed. Reg. 16332.

We think the procedures followed by the Commissioner were fundamentally defective.

The Commissioner acted pursuant to 21 C.F.R. § 130.14, the regulation establishing a summary judgment procedure for the Food and Drug Administration.[5] This regulation is modeled after Rule 56 of the Federal Rules of Civil Procedure, the summary judgment rule of the federal district courts. As counsel for the government stated at oral argument, the agency's procedure is analogous to the procedure under Rule 56. A vital distinction, however, is that the Commissioner here was not an impartial arbiter of the con-

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[5] 21 U.S.C. § 355(e) grants applicants the right to "due notice and opportunity for hearing" prior to withdrawal of approval to market new drugs in interstate commerce. We do not construe this section as precluding the use of summary judgment in appropriate circumstances, but it does restrict the application of that procedure to cases in which no material factual issue is presented and a hearing would be a hollow formality. *See Pennsylvania Gas and Water Co.* v. *Federal Power Comm'n*, No. 71-1126, 6-7 (D.C. Cir. decided May 2, 1972); *cf. Fidelity & Deposit Co.* v. *United States*, 187 U.S. 315, 320 (1902); 6 J. MOORE, FEDERAL PRACTICE § 56.06, at 2075-80 (2d ed. 1966).

See Gellhorn & Robinson, *Summary Judgment in Administrative Adjudication*, 84 Harv. L. Rev. 612 (1970), for a discussion of the use of summary procedures in administrative adjudications.

tentions of opposing parties, but was himself the moving party undertaking to support his own proposed order. The petitioner's applications had been approved, pursuant to 21 U.S.C.A. § 355(b) (1961), but now, under 21 U.S.C. § 355(e), the Commissioner proposed, without a hearing, to withdraw that approval on the basis of a new standard and new information, together with the evidence available when approval was originally granted. In this situation we think it was incumbent upon the Commissioner, before calling upon the petitioner for additional evidence establishing a right to a hearing, to state facts and reasons showing at least prima facie that the evidence before him raised no material issue of fact which would justify a hearing. This view of the Commissioner's burden is consistent with the practice under Rule 56 of the Federal Rules of Civil Procedure. Under that rule the moving party has the burden of presenting evidence that establishes his right to summary judgment as a matter of law; and he may not, by the bare assertion that he is entitled to summary judgment, shift to his opponent the burden of establishing the contrary. *Evers* v. *Buxbaum*, 102 U.S. App. D.C. 334, 253 F.2d 356 (1958); *Washington Post Co.* v. *Keogh*, 125 U.S. App. D.C. 32, 365 F.2d 965 (1966).

At no stage of this proceeding did the Commissioner present anything approaching a prima facie showing that there was no genuine and substantial issue of fact requiring a hearing. The reports of the NAS-NRC panels which we have quoted, and upon which the Commissioner relied in his notice of January 23, 1968, were cryptic and conclusory, without any statement of supporting facts. The Commissioner's notice of January 23, 1968 and his notice of July 10, 1968 parroted the language of the statute without reference to any evidence. In short, at no time did the Commissioner set forth the facts and reasons upon which he relied in reaching his conclusion that no material issue of fact existed. We think that such an application of the Commissioner's summary judgment rule is not in harmony with the

principle of the rule and is fundamentally unsound and unfair. Before calling upon the petitioner to answer, the Commissioner, as the moving party, had an obligation to present at least a prima facie case for denial of a hearing. *Cf. Greene* v. *McElroy*, 360 U.S. 474, 496 (1959); *Southern Railway Co.* v. *Virginia*, 290 U.S. 190, 197 (1933). Only after such a presentation could the Commissioner fairly impose upon the petitioner the heavy sanctions of 21 C.F.R. § 130.14.

By what we have said we do not intend to require a wholesale incorporation of the practice under the Federal Rules of Civil Procedure into administrative summary judgment proceedings; but the limited steps we have outlined are basic to administrative fairness.

The petitioner attacks the Commissioner's final order of withdrawal upon the further ground that it is not supported by adequate findings and conclusions. We agree. Both the statute, 21 U.S.C. § 355(e), and the Commissioner's own regulation, 21 C.F.R. § 130.14(b), require the Commissioner to state the findings upon which his order is based, and the summary judgment procedure did not excuse the Commissioner from that requirement. *Cf. NLRB* v. *Clement-Blythe Companies*, 415 F.2d 78, 81, 82 (4th Cir. 1969). Yet the Commissioner's order of October 15, 1970 merely tracks the language of the statute, stating in conclusory terms that there is a lack of substantial evidence that the petitioner's drugs are effective. As we have frequently emphasized, findings of fact are not mere procedural niceties; they are essential to the effective review of administrative decisions. Without findings of fact a reviewing court is unable to determine whether the decision reached by an administrative agency follows as a matter of law from the facts stated as its basis, and whether the facts so found have any substantial support in the evidence. *Saginaw Broadcasting Co.* v. *FCC*, 68 App. D.C. 282, 287, 96 F.2d 554, 559, *cert. denied*, 305 U.S. 613 (1938); *National Geographic Society* v. *District Unem-*

ployment Compensation Board, 141 U.S. App. D.C. 313, 438 F.2d 154 (1970); *Environmental Defense Fund, Inc.* v. *Hardin*, 138 U.S. App. D.C. 391, 397-98, 428 F.2d 1093, 1099-1100 (1970); *Greater Boston Television Corp.* v. *FCC*, 143 U.S. App. 383, 393, 444 F.2d 841, 851 (1970), *cert. denied*, 403 U.S. 923 (1971). Here we are left completely in the dark as to the facts and the evidence upon which the Commissioner based his judgment. Such a record cannot support the Commissioner's order.

Finally, the petitioner contends that the Commissioner acted arbitrarily by denying the petitioner's request for a stay and immediately thereafter entering a final order of withdrawal. Again, we agree. The request for a stay was not unreasonable and there is no suggestion that it was made in bad faith. In light of the leisurely if not dilatory pace at which the Commissioner had moved in the litigation —his failure to name a hearing examiner in response to the petitioner's demand of Augst 9, 1968, and his delay of more than two months in responding to the petitioner's August 7, 1970 request for a stay—the Commissioner's precipitous and summary action was arbitrary. In the circumstances we think petitioner was entitled to an opportunity to submit additional evidence or plead over when its request for a stay was denied. The Commissioner's explanation for his action, that further delay would serve no useful purpose, was a mere administrative ukase and amounted to no explanation at all.

We intimate no views as to the merits of this controversy over the effectiveness of the petitioner's drugs; the Commissioner's conclusions may well prove to be correct. We hold only that before entering his order he must conform to the requirements of administrative due process. This we think he has failed to do.

We set aside the Commissioner's order and remand the case for further proceedings in conformity with this opinion.

IT IS SO ORDERED.

APPENDIX I

Federal Food, Drug & Cosmetic Act (prior to October 10, 1962)
[Former Code Section Numbers Shown in Brackets]

Sec. 201[321]. For the purpose of this Act—

* * *

(p) The term "new drug" means—

(1) Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this chapter it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug the composition of which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780:

* * *

Sec. 107. (a) Except as otherwise provided in this section, the amendments made by the foregoing sections of this part A shall take effect on the date of enactment of this Act.

(b) The amendments made by sections 101, 103, 105, and 106 of this part A shall, with respect to any drug, take effect on the first day of the seventh calendar month following the month in which the Act is enacted.

(c) (1) As used in this subsection, the term "enactment date" means the date of enactment of this Act; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.

(2) An application filed pursuant to section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date by virtue of paragraph (2) of this subsection—

(A) the amendments made by this Act to section 201 (p), and to subsections (b) and (d) of section 505, of the basic Act, insofar as such amendments relate to the effectiveness of drugs, shall not, so long as approval of such application is not withdrawn or suspended pursuant to section 505(e) of that Act, apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application, but shall apply to any changed use, or conditions of use, prescribed, recommended, or suggested in its labeling, including such conditions of use as are the subject of an amendment or supplement to such application pending on, or filed after, the enactment date; and

(B) clause (3) of the first sentence of section 505(e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application (except with respect to such use, or conditions of use, as are the subject of an amendment or supplement to such approved application, which amendment or supplement has been

approved after the enactment date under section 505 of the basic Act as amended by this Act) until whichever of the following first occurs: (i) the expiration of the two-year period beginning with the enactment date; (ii) the effective date of an order under section 505(e) of the basic Act, other than clause (3) of the first sentence of such section 505(e), withdrawing or suspending the approval of such application.

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

Federal Food, Drug & Cosmetic Act (21 U.S.C.), as Amended [Code Section Numbers Shown in Brackets]:

Sec. 201[321]. For the purposes of this Act—

* * *

(p) the term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling con-

tained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

OPPOSITION BRIEF

No. 75-[illegible]

In the

Supreme Court of the United States

October Term, 1975

ELLIOT RICHARDSON, Secretary of Health, Education and Welfare, and CHARLES C. EDWARD, Commissioner of Food and Drugs,

Petitioners,

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED,

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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BRIEF FOR HYNSON, WESTCOTT AND DUNNING, INCORPORATED, IN OPPOSITION

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21 C.F.R. 130.14, as amended, 35 F.R. 7252	3, 6
Miscellaneous:	
Gellhorn and Robinson, *Summary Judgment in Administrative Adjudication*, 84 Harvard Law Review 612 (1971)	16, 17

IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-394

ELLIOT RICHARDSON, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners,

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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BRIEF FOR HYNSON, WESTCOTT AND DUNNING, INCORPORATED, IN OPPOSITION

OPINIONS BELOW

The Opinion of the Court of Appeals (Pet., App. A, 1a) is reported at 461 F.2d 215. The Order of the Commissioner of Food and Drugs reviewed by the Court of Appeals was published in the Federal Register of June 18, 1971 (36 F.R. 11763, Pet., App. C, 14a-22a).

JURISDICTION

The judgment of the Court of Appeals was entered on May 24, 1972 (Pet., App. B, 12a). Mr. Justice Rehnquist extended the time to file a petition for certiorari to September 7, 1972. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1) and 21 U.S.C. 355(h).

STATUTES AND REGULATIONS INVOLVED

Section 505(e) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(e)) provides in part:

> "The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds * * * (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof * * *.

Section 505(d) (21 U.S.C. 355(d)) provides in pertinent part:

> * * * As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling or proposed labeling thereof.

Pertinent provisions of the regulations of the Commissioner of Food and Drugs, 21 C.F.R. 130.12(a)(5) and 130.14, as amended, 35 F.R. 7251, 7252, are set forth in Appendix A, infra, 1a.

QUESTIONS PRESENTED

Whether, despite the evidence submitted by Hynson, Westcott & Dunning, Incorporated, the Commissioner of Food and Drugs may, without a hearing, make a determination that there is a lack of substantial evidence of effectiveness of the drug Lutrexin, within the meaning of the Federal Food, Drug and Cosmetic Act (as amended by the Drug Admendments of 1962) and the Commissioner's regulations and, upon the basis of such determination, withdraw approval of the new drug application for such drug.

If the Government's petition should be granted we would want to place the following additional questions before this court which were argued in the court below:

1. Whether Hynson, Westcott & Dunning was entitled to a hearing by virtue of its timely acceptance of the proffered opportunity for a hearing under regulations then in effect, regardless of its rights under the regulations thereafter adopted under which a hearing was denied.
2. Whether the regulations under which a hearing was denied are valid.

STATEMENT

A. In the Statement in its petition the Government refers to "the mass of material" submitted by Hynson, Westcott & Dunning (HW&D) to the Food and Drug Administration (FDA) upon which the company relied as "substantial evidence" of effectiveness, declaring that

"Most of that material had previously been considered by the NAS-NRC panel" which found Lutrexin "possibly effective" (Pet. 9); and thereafter stating that the NAS-NRC panel had "little difficulty" concluding that the studies submitted "did not meet the medical community's standard of adequacy." (Pet. 14.)

In fact, only three of the fourteen studies (of which eleven were published), were considered by the NAS-NRC panel, *viz.*, two studies not identified by the panel by name and the study by S. S. Jones, *Lututrin, A New Drug for Relief of Dysmenorrhea.* (JA II, 92). None of the other studies (JA II, 1 et seq.) was considered.[1]

Of course, the affidavits of experts filed in HW&D's action in the District of Maryland (JA I, 38-94) were not before the NAS-NRC panel, having been executed long after the report of the panel was made to FDA.

The Government states that the Commissioner of FDA "demonstrated how each [study] showed deficiencies on its face that prevented it, under the rules, from being treated as an adequate and well-controlled study" (Pet. 9). This demonstration was not, however, convincing to the Fourth Circuit which thought that "whether the studies were as controlled as they might have been and whether there was a failure in these studies as published to fill in all the details the Commissioner might think appropriate are matters that could be developed at a hearing, after the authors were examined and the reliability of the investigations further inquired into" (461 F.2d 215 at 221-222; Pet. 1a, at 11a).

B. HW&D, in its Cross-petition for certiorari, filed on September 11, 1972, (No. 72-414) has presented questions of concern to many manufacturers and shippers of drugs, and to physicians who prescribe them, as con-

[1] Two of the studies were completed after the panel reported.

trasted with the matter before the court in the instant case, which involves essentially the question of whether the Commissioner acted arbitrarily in denying a hearing to HW&D on the particular facts before him.

ARGUMENT

Introduction

The Government's statement of the Question Presented is unacceptable in two respects. First, it assumes a failure to comply with the Commissioner's regulations and asks whether in such a case approval of a new drug application could be withdrawn without a hearing, thereby completely ignoring the matter of whether, in fact, there was such a failure to comply. Secondly, the Question is phrased as if there were involved a general principle of law of broad application whereas the real question is whether, *on the particular facts of this case*, the Commissioner could properly determine without a hearing that there was a failure to comply with the regulations.

This is not a case where the evidence, on its face, does not meet the applicable standards and therefore there are no facts to ascertain.[2] We shall show that the studies submitted by HW&D were of sufficient stature to require a hearing to determine whether they meet the standard of the FDA regulation, and that the Court's conclusion was correct that they raised a genuine and substantial issue of material fact as to the effectiveness of Lutrexin, within the meaning of the regulations.

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[2] As in *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192 (1956), where petitioner concededly "owned" more television stations than a rule of the Federal Communications Commission permitted; and *Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33 (1964), where a petition was patently not in proper form because of certain price-changing provisions in the contracts filed with the petition, which were not permissible under a rule of the Commission.

I

THE COURT OF APPEALS WAS PLAINLY RIGHT IN HOLDING THAT HW&D HAD SUBMITTED TO FDA EVIDENCE RAISING A GENUINE AND SUBSTANTIAL ISSUE OF MATERIAL FACT ENTITLING HW&D TO A HEARING PRIOR TO WITHDRAWAL OF APPROVAL OF THE NDA FOR LUTREXIN.

FDA's regulations provide that in order for an NDA applicant to be entitled to a hearing on a proposal by the Commissioner of Food and Drugs to withdraw approval of an NDA, the applicant must come forward with "specific facts showing there is a genuine and substantial issue of fact that requires a hearing;" and the absence of adequate and well-controlled investigations to support claims of effectiveness is cited by FDA as an example of a defect in a request for a hearing which would result in denial of the request (21 CFR 130.14(b), App. A, infra, 4a). The regulations spell out in detail the principles FDA considers "essentials of adequate and well-controlled clinical investigations" (21 CFR 130.12 (a) (5), App. A, infra, 1a).

In the instant case, the Commissioner concluded that HW&D's response to the notice of hearing (JA I, 27) did not show that there was a genuine and substantial issue of fact which justified the holding of a hearing (Pet. App. C, 14a). The court below held that FDA erred in denying HW&D a hearing because the data submitted by the company did show the existence of a genuine and substantial issue of fact. For the reasons stated below we submit the court was plainly correct.

A. The Affidavits And Reports Of Medical Investigations Are Adequate Justification For A Hearing.

HW&D submitted with its response to the notice of hearing affidavits of six physician-experts in the field of

obstetrics and gynecology (OB/GYN)[3]. As noted by the court below, the government ". . . did not impugn the competency or qualifications" of these experts. "Their professional qualifications, as they appear in the record are impressive."[4] The six OB/GYN physicians have had extensive experience with Lutrexin in the treatment of dysmenorrhea and premature labor[5]. The affidavits show that the doctors have used Lutrexin in the treatment of a total of approximately three thousand patients with these disorders over the past fifteen years. The affidavits state without equivocation that Lutrexin is safe and effective for its intended uses.

The affiants' conclusions were not based merely on their clinical experience with Lutrexin, but also upon studies reported in the medical literature.[6] Eleven reports on Lutrexin have been published in authoritative professional medical journals and were submitted to FDA in support of HW&D's "request" for a hearing. Two unpublished investigations by OB/GYN experts were also placed before the agency. These studies provide a sound basis for the conclusions of HW&D's affiants that Lutrexin is both safe and effective for use in the treatment of dysmenorrhea and premature labor. For example, Dr. Gratton's paper[7] on Lutrexin reports on a study of 219 patients with a medical history of prior pregnancies tragically interrupted by miscarriage or premature labor.

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[3] JA I, 38-94.

[4] 461 F.2d 215, 221, Pet., App. B at 27a.

[5] Premature labor and dysmenorrhea are generally thought to result, at least in part, from abnormal or untimely contractions of the musculature of the uterus. The purpose of Lutrexin therapy is to quiet the uterus to prevent, in premature labor, a too-early birth, and, in dysmenorrhea, to relieve cramping and associated symptoms.

[6] These studies are reproduced in JA II.

[7] JA II, 1.

Less than 50% viable babies resulted from the prior untreated pregnancies of these patients. With use of Lutrexin, almost 80% viable babies were obtained. Dr. Rezek's paper[8] presents 54 cases of premature labor treated with Lutrexin. Premature labor was stopped in 74% of the patients for at least 28 days, thus ". . . enabl . . . [ing] many fetuses to survive that otherwise would have died because of prematurity" (JA II, 41). Other studies reported in the medical literature and submitted to FDA, demonstrate the safety and effectiveness of Lutrexin for use in treatment of dysmenorrhea,[9] and attest to the biological availability of the drug.[10]

B. FDA's Findings Concerning HW&D's Affidavits And Medical Studies Demonstrate The Existence Of Genuine And Substantial Issues Of Fact Requiring A Hearing.

In his order (Pet., App. C, 14a et seq.) withdrawing approval of the NDA for Lutrexin, the Commissioner denied HW&D a hearing on its contentions that the drug was not a new drug and that substantial evidence of effectiveness existed for the product, basing the denial primarily on the ground that no adequate and well-controlled clinical investigations had been proffered by HW&D. The Commissioner attempted to support the determination by a critique of the data submitted by HW&D, purporting to single out deficiencies in the design and performance of the investigations. The Court below made no distinction between the Commission's analysis of the studies in connection with HW&D's "new drug" contention (Pet. App. C, 16a-20a) and the analysis of the studies in connection with the "substantial evidence" contention (id. 20a-21a). For the purposes of

[8] JA II, 40.

[9] JA II, 33, 85, 92.

[10] JA II, 34 at 38, and 85 at 87 and 90.

this discussion, no distinction will be made between the two points involved." [11]

The Commissioner's analysis of HW&D's medical investigations raises substantial and complex issues of fact which cannot, as we shall show, appropriately be resolved by a reviewing court without the benefit of a record based upon expert evidence adduced at a hearing before FDA. This is not a case like *Pfizer, Inc.* v. *Richardson*, 434 F.2d 536 (2d Cir. 1970) where the court could say ". . . it is apparent even to us laymen that the FDA had a reasonable basis for considering that Pfizer's submissions did not comply with the requirement of the statute and the Regulation" (434 F.2d at 546-547). Nor is it a case like *Upjohn Company* v. *Finch*, 422 F.2d 944 (6th Cir. 1970) where the company, according to FDA's final order, recognized that its studies did not meet the adequate and well-controlled criteria in FDA's regulations but argued that the studies plus clinical experience with its drugs amounted to substantial evidence (422 F.2d at 958).[12] The instant case, by contrast, involves medical

[11] There is, however, a fundamental distinction of importance, shown in HW&D's Cross-Petition herein, (No. 72-414), between the evidence required for proof of general recognition of safety and effectiveness, the test for a "new drug", and proof of actual effectiveness by adequate and well-controlled studies, the substantial evidence test. As was pointed out in our briefs in the court below, there is no basis in the statute or legal precedent, for the proposition that substantial evidence of effectiveness must be shown to prove a product not to be a new drug. The courts have specifically rejected the proposition. *United States* v. *Articles of Drug Labeled "Quick O-ver"*, 274 F. Supp. 443, 445-446 (D. MD. 1967); *Amp Incorporated* v. *Gardner*, 389 F.2d 825, 831 (2d Cir. 1968), cert. denied sub nom *Amp. Inc.* v. *Cohen*, 393 U.S. 825, rehearing denied 395 U.S. 917; *United States* v. *An Article of Drug*** Excedrin P.M.*, CCH Food, Drug & Cosmetic Law Reporter 40, 486 at page 41, 226 (D. N.Y. 1971, No. 70-C-77); *United States* v. *Article of Drug, Etc.*, 294 F. Supp. 1307, 1310 (D. Ga. 1968).

[12] In *Upjohn* the agency permitted the company to make an oral presentation on the factual issues involved.

evidence which, as we shall show, cannot on its face be reasonably judged as failing to meet the requirement of "substantial evidence". Encompassed within this issue is the factual and legal question, raised in HW&D's affidavits, of whether medical ethics proscribe investigations other than the type submitted by HW&D.

(1) *Historical Controls*

FDA's regulations defining "adequate and well-controlled studies" require that a medical investigation contain a method of selection of the subjects that ". . . provides a comparison of the results of treatment . . . [using the drug under investigation] with a control in such a fashion as to permit quantitative evaluation" (21 C.F.R. 130.12(a)(5)(ii)(a)(4), App. A, infra, 1a-2a). One method of control acceptable to the agency is historical control:

> "Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen . . . the effectiveness of which is established" (21 C.F.R. 130-.12(a)(5)(ii)(a)(4)(iv), App. A, infra, 3a).

It cannot be gainsaid that premature labor and threatened and habitual abortion are conditions involving a "high and predictable mortality" as well as conditions "where morbidity is predictable." If premature contractions of a gravid uterus are not halted, a dead fetus is certain.

The necessity of performing certain tests using historical controls is described by Dr. Allen who was a member of the NAS/NRC panel which reviewed Lutrexin:[13]

> "There is a good deal of uncertainty regarding what type of study should be carried out in order to fully establish the validity of the results. In these studies the patient herself serves as the control; the results in the pregnancies prior to the treated pregnancy are compared with the results in the treated pregnancy. A supposedly better method of study which is popular today would utilize the placebo method; one patient receives the hormone and the next patient the placebo, the investigator not knowing which patient received the placebo until the study is complete. This type of study is now so 'sacred' that any other type is often not recognized as investigative. However, there are many clincial problems in which this type of study violates the rules of clinical morality as well as common sense. Let us consider some disease in which the risk of death is appreciable, lobar pneumonia, for example. No clinician could risk treating alternate cases with an antibiotic and a placebo. In such a study the risk of death while receiving the placebo might be as much as 25 per cent. In the study of habitual abortion the risk of death to the fetus in

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[13] Dr. Allen also is on record in support of the continued marketing of Lutrexin. He has stated, in a notarized letter to HW&D:

> "Lutrexin contains a biologically active component (as yet unidentified structurally) which has a relaxing effect on the uterus of laboratory animals and women". * * * "The clinical evidence which you have submitted [to me] . . . does indicate that Lutrexin is beneficial in the three conditions for which it is recommended. The evidence also indicates that Lutrexin is not harmful or dangerous either to the patient or to the fetus. You have submitted no evidence that Lutrexin is ineffective, nor do I know of any evidence in the medical literature indicating that it is ineffective." * * * "Lutrexin, since it contains an active principal which relaxes the uterus, should be available for the treatment of premature labor . . ." JA I, 60-61.

utero is between 80 to 90 per cent. It seems to me that one no longer has the right to use a placebo as a control because the data already available from the studies in which the patient serves as her own control indicate that the fetal losses are reduced from 80 or 90 per cent to 25 per cent or perhaps less."[14]

HW&D's Investigations

In Dr. Gratton's study,[15] which involved habitual aborters, the patients were used as their own controls, and the results of Lutrexin treatment vis a vis prior untreated pregnancies were statistically evaluated:

". . . in the 219 patients with a total of 446 pregnancies, there were only 46% live births prior to the use of Lutrexin. Following the administration of Lutrexin, the percentage of live births in these same patients was 79.8% with a probability of .001. Probabilities ranging from .001 to .05 were observed in women with one to five pregnancies who had been treated with Lutrexin" (JA II, 2-3).

In Dr. Majewski's first two studies,[16] which involved premature labor, the results were compared with the documented history of premature births in the hospital where the study was performed:

"The hospital wherein the study was conducted has . . . a premature birth rate of 9.7 per cent by length of gestation and 6.2 per cent by weight. During a four-month period in 1953, the premature birth rate by history was 9.7 per cent in 1601 deliveries. During the same period, there were 101 premature births by weight, or 6.3 per cent. During this study there were, in a comparable period during 1954, 154 births premature by history in a total of 1631 deliveries,

[14] JA II, 52-53. This paper is not a report on Lutrexin.

[15] JA II, 1.

[16] JA II, 7, 15.

> for a percentage of 9.4. In our series of patients using the uterine relaxing factor [Lutrexin] the number of premature deliveries by weight was reduced during these four months to 80 (4.9 per cent), a saving of 21 premature deliveries" (JA II, 9).

In Dr. Majewski's second study,[17] which is a continuation of the first study, the comparison was enlarged to one of the total number of premature survivals, stillbirths and neonatal deaths during the 15-month period the study was in progress. In Dr. Majewski's third study the results were compared statistically with the results of prior untreated pregnancies (JA II, 29).

The studies by Drs. Rezek, Gray, Trythall, G. Jones et al., and S. Jones do not purport to be controlled studies,[18] but they are "clinical investigations" within the meaning of the definition of "substantial evidence" in Section 505(d) and should be so recognized by FDA. Instead, the FDA regulations merely state that such investigations "may provide corroborative support of well-controlled studies regarding efficancy and may yield valuable data regarding efficacy of the test drug" (21 C.F.R. 130.12(a)(5)(ii)(c), App. A, infra, 1a).

FDA's Findings

We have referred to the fact that, in its withdrawal order, FDA offered a critique of the HW&D studies to support its conclusion that they were not adequate and well-controlled investigations and, therefore, that no hearing was required. A review of some of the specifics of the critique clearly reveals, however, that genuine and substantial issues of fact do exist between FDA and HW&D. FDA said, for example:

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[17] JA II, 15.

[18] The G. Jones et al study (JA II, 85) does, however, contain a small controlled study of the biological availability of Lutrexin.

(1) With respect to Dr. Majewski's first two studies:[19] "* * * Six patients received the drug for less than three hours, which the authors without explanation considered too short a time for a true test of effectiveness". (Pet. App. C, at 17a);

(2) With respect to Dr. Majewski's third study:[20] "Substantiating documentation to establish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided. * * * The data in Table I does not admit of statistical evaluation by the chi square test since the test is based on the assumption that each number in the columns of Table I is the sum of independent yes or no responses . . ." (Pet., App. C, at 18a).

(3) With respect to Dr. Rezek's first study:[21] Concomitant medication is not excluded * * * No explanations of the methods of observation, the recording of results, and steps taken to minimize patient and investigator bias are provided" * * * (Pet., App. C at 19a).

(4) With respect to Dr. Gratton's study:[22] The pairings of live births percentages in Table II cannot be compared since the number of previous pregnancies differs between the pair percentages and there is no data on possible etiologic factors of previous abortions and premature labor" (Pet., App. C at 19a).

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[19] JA II, 7, 15.

[20] JA II, 23.

[21] JA II, 34.

[22] JA II, 1.

These purport to be findings of facts which obviously are considered material by FDA.

These unsupported findings raise issues of fact which can only be resolved by expert testimony at a hearing before FDA. As stated by the Court below:

> "Assuming that all the objections by the Commissioner . . . may have some validity, they do not justify a final conclusion . . . that it 'clearly appears' that there is no genuine issue of fact . . .; at most, they merely create a genuine question of fact to be resolved at a hearing upon proper evidence" (Pet., App. A, 11a).

Without the benefit of a full record based upon expert testimony as to the medical and scientific validity of FDA's objections and the affidavits and studies themselves, a reviewing court is not in a position to decide the complex questions involved. Criticisms such as "the data . . . does not admit of statistical evaluation by the chi-square test . . ." raise questions of fact which can be resolved only by experts. Under the circumstances of this case, FDA's order cannot be given the usual deference accorded orders of "expert" administrative agencies; nor are its findings of fact to be considered conclusive under Section 505(h), because the order is not based upon substantial evidence of record adduced at an adjudicative hearing before the agency.

II

THE NATURE OF THE FDA "SUMMARY DECISION" PROCEDURES EMPHASIZES THE NECESSITY FOR A HEARING ON THE EFFECTIVENESS OF LUTREXIN.

HW&D argued in the Court below that FDA, under its procedures (App. A, 4a) is both litigant and judge; that FDA argues, as a litigant, that no genuine issue

of fact exists and then, proceeds, as judge, to uphold its own argument; and that such a combination of advocating and judging violates fundamental principles of fairness and due process.

Given this kind of procedure it is submitted that, at the very least a hearing is required at which the experts can be examined to determine whether their studies constitute substantial evidence of the effectiveness of Lotrexin and at which they can explain the basis for the opinions set forth in their affidavits. As the Court of Appeals for the District of Columbia circuit recently said, with reference to the same FDA procedure:

> "As counsel for the government stated at oral argument, the agency's procedure is analagous [sic] to the procedure under Rule 56. A vital distinction, however, is that the Commissioner here was not an impartial arbiter of the contentions of opposing parties, but was himself the moving party undertaking to support his own proposed order." [23]

We are aware that some agencies, including the Federal Trade Commission and the National Labor Relations Board, provide for administrative summary decision or judgment in their regulations; [24] and that the Administrative Conference of the United States recommended a rule for summary decision in agency adjudication at its Fourth Plenary Session, June 2-3, 1970, in Washington, D.C.[25] These agency regulations and the Administrative Conference recommendation, however, contemplate that

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[23] *USV Pharmaceutical Corporation* v. *Secretary of Health, Education and Welfare*, No. 24, 900, D.C. Cir., decided August 14, 1972 (Slip op., p. 11).

[24] FTC: 16 C.F.R. 3.24; NLRB: 29 C.F.R. 102.24-28, in particular section 102.24.

[25] The recommendation (No. 20) is set forth in Gellhorn and Robinson, *Summary Judgment in Administrative Adjudication*, 84 Harvard Law Review 612, 628-629 (1971).

the party desiring summary decision make a motion for such a decision before a hearing examiner or presiding officer appointed to conduct the hearing and that the essential facts upon which the motion is based be placed before the examiner, who may call for argument and the submission of briefs.

The FDA regulations, although purportedly based upon Civil Rule 56, make no provision for such procedure. No examiner is appointed to hear an FDA motion and no affidavits or other evidence are presented by FDA to show the absence of a genuine and substantial issue of material fact. FDA simply decides that there is no such issue.

Moreover, no discovery procedures are provided by FDA to the party opposing summary decision. Yet, concededly, the summary decision rule is inapplicable to proceedings lacking or restricting discovery procedures.[26]

It is clear that a basic motivation, if not the principal one, for the FDA order withdrawing approval of the NDA for Lutrexin was the opinion of the NAS-NRC panel that Lutrexin was "possibly effective" and that the claims for the drug were not adequately supported. In fact, the report of the panel was the only "evidence" before FDA other than that provided by HW&D.

As we have noted, only three of the reports of the fourteen studies set forth in Volume I of the Joint Appendix were before the panel. It was therefore important to HW&D to inquire into the decision-making process which led to the withdrawal order. In response to inquiry by HW&D, dated August 18, 1969, the Acting

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[26] Gellhorn & Robinson, *Summary Judgment in Adjudication*, supra, at 618. The authors note (p. 618, footnote 29): "In the federal courts summary judgment has long been denied where the party opposing the motion is barred from access to rebuttal information . . ."

Associate Director of Information for Public Services of the Department of Health, Education and Welfare replied, by letter of September 18, 1969 (see Appendix B, infra, 6a et seq.), that neither FDA nor the Department has "any report of any deliberations, minutes, notes, or other material of the National Academy of Sciences—National Research Council Panel . . ."; that neither FDA nor the Department "has any statement, other than the reports themselves, reflecting the view of each member of the panel concerning the effectiveness of Lutrexin . . ."; [27] that "other than the references listed under the heading, Documentation, by the Panel in its reports on Lutrexin . . . we do not know what medical or scientific literature was relied upon by the Panel"; and that FDA "has not conducted any independent clinical study or other scientific investigation of Lutrexin . . . at any time."

Thus, one of the principal supports of the FDA withdrawal order was formulated without the benefit of most of the available literature on Lutrexin and we do not know how or by what vote the panel reached its decision. Had the NAS-NRC panel had the benefit of such literature reflecting the conclusions that the clinical experts have reached, its evaluation would, we believe, have been that the drug is effective as claimed. The final evaluation of FDA might therefore have been entirely different. All that HW&D asks this Court, therefore, in this brief, is that the government's petition be denied so that the experts can be examined at a hearing to determine the validity and significance of their studies and of the opinions expressed in their affidavits.

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[27] This point was important because, of the five members of the panel, only two were specialists in Obstetrics and Gynecology.

III

THE ESTABLISHED CRITERIA FOR REVIEW BY THIS COURT ARE NOT MET IN THIS CASE.

The Government states that the evidence on which the court here relied "is a type of evidence that very likely can be produced by the manufacturer in virtually every withdrawal proceeding" (Pet. 16). The facts do not support that statement. Thus, in similar situations no evidence comparable to that submitted by HW&D was submitted to FDA by Ciba-Geigy Corporation (see *Ciba-Geigy Corp.* v. *Richardson*, 446 F.2d 466, 467 (2d Cir. 1971)), or by American Cyanamid Company (see *American Cyanamid Company* v. *Richardson*, 456 F.2d 509, 511-12 (1st Cir. 1971).

The cases just cited, together with *Upjohn Company* v. *Finch*, 422 F.2d 944 (6th Cir. 1970) and *Pfizer, Inc.* v. *Richardson*, 434 F.2d 536 (2d Cir. 1970), cited by the government, emphasize the point made at the outset of this Argument: that there is involved here, not a general principal of law of broad application, but the question whether, on the particular facts of this case, the Commissioner could properly determine without a hearing that there was a failure to comply with FDA regulations.

In *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192 (1956) and *Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33 (1964), it was held that an agency may refuse a hearing upon applications which fail to conform to criteria established by regulations pursuant to the pertinent statute; but in those cases it was neither conceded nor obvious that the applications failed to conform.

The Government also cites *Ciba-Geigy Corp.* v. *Richardson*, supra, where failure to conform to the rule was obvious. There the court said:

> "In the present case Ciba could have obtained a hearing simply by compiling and presenting the evidence needed to make out a prima facie case. No valid reason is offered for its not doing so. Thus it was afforded the opportunity for a hearing to which it was entitled under Section 505(e) of the Act, 21 U.S.C. Section 355(3)" (466 F.2d at 468).

The courts in *Upjohn* and *Pfizer* were satisfied that the evidence before the Commission brought those cases within the principal enunciated in *Storer*, *Texaco* and *Ciba* and there was reason for this view, as discussed in Point I, supra. The facts before the Commissioner in each of the FDA cases discussed (*Ciba-Geigy*, *American Cyanamid*, *Upjohn* and *Pfizer*) were different and the facts in the instant case are different from those in the other cases cited.

In the instant case, we believe that the Court of Appeals for the Fourth Circuit was correct in its conclusion that the evidence presented a genuine and substantial issue of material fact, for the reasons stated in Point I.

We conclude, therefore, that the decision does not, as the Government states (Pet. 19) conflict with *Pfizer, Inc.* v. *Richardson* or *Upjohn Co.* v. *Finch*, supra, or with *Pharmaceutical Manufacturers Ass'n.* v. *Richardson*, 318 F. Supp. 301 (D. Del., 1970).[28]

The Government expresses apprehension that, if the basis of the reasoning and decision of the court below is adopted, FDA would be swamped with hearings. Even

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[28] This was an action for declaratory and injunctive relief in which the FDA regulations were upheld. The court there specifically distinguished the "abstract setting as presented here" from a "definitive factual situation" where the reviewing Court could determine whether the Commissioner correctly applied his regulations (318 F. Supp. 301 at 313).

if true, this is not of itself a valid reason for denying HW&D a hearing. As the Court of Appeals for the Third Circuit said in *Mississippi River Fuel Corp.* v. *Federal Power Commission*, 202 F.2d 899 (3d Cir. 1953):

> "We can understand, as the argument in this case has seemed to imply, that the Commission may have had to contemplate serious injury to the public interest because of its inability with very limited funds and staff to perform the enormous task of investigation and analysis imposed upon it in times when so many public utilities are submitting important proposals within its jurisdiction and the statutory scheme requires it to act promptly or let proposals go by default. But the remedy lies with Congress. If changes in the law are needed, or more personnel to administer existing law, or both, it is not for the administrative agency or the courts to try to make up for this deficiency by taking unauthorized short cuts or indulging time saving procedures which fail to accord parties the rights which the law as written gives them." (202 F.2d at 902-903).

In any event, the question whether, on complex medical facts which vary from case to case, the Commissioner is justified in concluding that no genuine and substantial issue of material fact was present, does not seem to be the kind of matter which qualifies for review by this Court. On this point the Court has said:

> ". . . it is very important that we be consistent in not granting the writ of certiorari except in cases involving principles the settlement of which is of importance to the public, as distinguished from that of the parties, and in cases where there is a real and embarrassing conflict of opinion and authority between the Circuit Courts of Appeals." [20]

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[20] *Layne & Bowler Corporation* v. *Western Well Works*, 261 U.S. 387, 393 (1923).

CONCLUSION

For the foregoing reasons it is submitted that the petition for certiorari should be denied.

Respectfully submitted,

EDWARD BROWN WILLIAMS

Counsel for Hynson, Westcott & Dunning, Incorporated

APPENDIX A

21 C.F.R. 130.12(a)(5), as amended, 35 F.R. 7251, provides:

§ 130.12 Refusal to approve the application.

(a) * * *

(5) (i) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(ii) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is "substantial evidence" to support the claims of effectiveness for "new drugs" and antibiotic drugs.

(*a*) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:

(*1*) A clear statement of the objectives of the study.

(*2*) A method of selection of the subjects that—

(*i*) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic

criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired.

(*ii*) Assigns the subjects to test groups in such a way as to minimize bias.

(*iii*) Assures comparability in test and control groups of pertinent variables, such as age, sex, severity, or duration of disease, and use of drugs other than the test drug.

(*3*) Explains the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subjective response, and steps taken to minimize bias on the part of the subject and observer.

(*4*) Provides a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. Level and methods of "blinding," if used, are to be documented. Generally, four types of comparison are recognized:

(*i*) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients.

(*ii*) Placebo control: Comparison of the results of use of the new drug entity with an inactive preparation designed to resemble the test drug as far as possible.

(*iii*) Active treatment control: An effective regimen of therapy may be used for comparison, e.g.,

where the condition treated is such that no treatment or administration of a placebo would be contrary to the interest of the patient.

(*iv*) Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen (therapeutic, diagnostic, prophylactic) the effectiveness of which is established.

(*5*) A summary of the methods of analysis and an evaluation of data derived from the study, including any appropriate statistical methods.

Provided, however, That any of the above criteria may be waived in whole or in part, either prior to the investigation or in the evaluation of a completed study, by the Director of the Bureau of Drugs with respect to a specific clinical investigation; a petition for such a waiver may be filed by any person who would be adversely affected by the application of the criteria to a particular clinical investigation; the petition should show that some or all of the criteria are not reasonably applicable to the investigation and that alternative procedures can be, or have been, followed, the results of which will or have yielded data that can and should be accepted as substantial evidence of the drug's effectiveness. A petition for a waiver shall set forth clearly and concisely the specific provision or provisions in the criteria from

which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been, employed, what results have been obtained, and the basis on which it can be, or has been, concluded that the clinical investigation will or has yielded substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(*b*) For such an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(*c*) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

* * * *

21 C.F.R. 130.14(b), as amended, 35 F.R. 7252, provides:

§ 130.14 Contents of notice of hearing.

* * * *

(b) If the applicant elects to avail himself of the opportunity for a hearing, he is required to file a

written appearance requesting the hearing within 30 days after the publication of the notice and giving the reason why the application should not be refused or should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition to the notice of opportunity for a hearing. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application, e.g., no adequate and well-controlled clinical investigations to support the claims of effectiveness have been identified, the Commissioner will enter an order on this data, making findings and conclusions on such data. If a hearing is requested and is justified by the applicant's response to the notice of hearing, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence, not more than 90 days after the expiration of such 30 days unless the hearing examiner and the applicant otherwise agree.

* * * *

APPENDIX B

[SEAL]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Sep. 18, 1969

J. H. Fitzgerald Dunning, President
Hynson, Westcott & Dunning, Inc.
Pharmaceutical Laboratory
Baltimore, Maryland 21201

Dear Mr. Dunning:

This is in further response to your letter of August 18, 1969, requesting information pertaining to the report of the Panel on Drugs Used in Disturbances of the Reproductive System, National Academy of Sciences-National Research Council, on the products Lutrexin Tablets and Trexinest Tablets. Our reply to your specific requests is as follows:

1. Neither the United States Food and Drug Administration, the Consumer Protection and Environmental Health Service, nor the Department of Health, Education, and Welfare has a Curriculum Vitae of the chairman and members of the Panel.

2. A copy of the Panel report on Trexinest Tablets is enclosed.

3. Copies of the contract between the Food and Drug Administration of the National Academy of Sciences-National Research Council, Contract No. FDA 66-197 (NEG), dated April 29, 1966, and Supplemental Agreement No. 1, dated June 17, 1966, are enclosed.

4. No instructions were issued by the Food and Drug Administration or the Department of Health, Education, and Welfare other than the contract itself.

5. The Department of Health, Education, and Welfare and the Food and Drug Administration issued no instructions or guidelines to the Panel on Drugs Used in Disturbances of the Reproductive System, nor did they communicate in any way with the Panel respecting any efficacy study of any product, including Lutrexin Tablets and Trexinest Tablets. As far as this Department is aware, the only instructions to the Panel are found in the document, Guidelines for the Drug Efficacy Study of the National Academy of Sciences-National Research Council; a copy of those "Guidelines" is enclosed.

6. The Food and Drug Administration, the Consumer Protection and Environmental Health Service, and the Department of Health, Education, and Welfare do not have any report of any deliberations, minutes, notes, or other material of the National Academy of Sciences-National Research Council Panel. The National Academy of Sciences-National Research Council Drug Efficacy Study Group may be able to inform you whether or not such documents exist.

7. Other than the references listed under the heading, Documentation, by the Panel in its reports on Lutrexin and Trexinest, we do not know what medical or scientific literature was relied upon by the Panel.

8. Neither the Food and Drug Administration, the Consumer Protection and Environmental Health Service, nor the Department of Health, Education, and Welfare has any statement, other than the reports themselves, reflecting the view of each member of the Panel concerning the effectiveness of Lutrexin and Trexinest.

9.-11. We have no information concerning whether the Panel solicited opinions from outside consultants, the manner in which the Panel's conclusion was reached, or whether any independent clinical studies of the effectiveness of Lutrexin and Trexinest were made by the Panel or on its behalf.

12. The Food and Drug Administration has not conducted any independent clinical study or other scientific investigation of the effectiveness of Lutrexin and Trexinest at any time.

13. (a) and (b) The information submitted by your firm to the Food and Drug Administration by letters dated July 22, 1968, and November 1968 was not submitted to the Panel, since the Panel had concluded its report and had it submitted to the Food and Drug Administration prior to May 23, 1968, the date the report was sent to your firm.

(c) Your firm has elected to avail itself of the opportunity for a hearing on the question of withdrawal of approval of the New Drug Applications for Lutrexin and Trexinest. As you know, there is no provision for prehearing discovery in the rules of practice which govern such hearings. Written reports and memoranda prepared by Food and Drug Administration personnel prior to the issuance of the Federal Register announced affording your firm an opportunity for a hearing on the withdrawal of the approval of the New Drug Applications for these drugs are internal-working papers which are specifically exempt from disclosure by the Public Information Act, 5 U.S.C. 552(b)(5). The official responsible for the final decision of any Food and Drug Administration action is Dr. Herbert L. Ley, Jr., Commissioner of Food and Drugs.

Sincerely yours,

/s/ Morton A. Lebow
MORTON A. LEBOW
Acting Associate Director of
Information for Public
Services

In the Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-414

HYNSON, WESTCOTT & DUNNING, INCORPORATED,
CROSS-PETITIONER

v.

ELLIOT RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

MEMORANDUM FOR THE RESPONDENTS

In *Richardson* v. *Hynson, Westcott & Dunning, Inc.*, No. 72-394, the government has petitioned for a writ of certiorari to review the decision of the court of appeals in this case that the Food and Drug Administration (FDA) was required to give Hynson, Westcott & Dunning ("Hynson") an evidentiary hearing prior to withdrawing approval of its New Drug Application (NDA) for the marketing of its drug product, Lutrexin, for failure to meet the efficacy requirements of the 1962 amendments to the Federal Food,

487-365—72

Drug, and Cosmetic Act of 1938. That petition raises an important question regarding the ability of the agency, without being required to hold evidentiary hearings, to withdraw marketing authority for numerous drugs for which no prima facie showing of effectiveness in accordance with the statutory standard of "substantial evidence" can be made.

The cross-petition raises threshold questions relating to the applicability of the drug efficacy and "substantial evidence" requirements to Lutrexin. These threshold questions are not peculiar to Lutrexin, but are bound to arise in connection with numerous other drugs that are potentially subject to withdrawal of NDA's under the efficacy requirements of the 1962 amendments. We believe that these issues are fairly raised by this case and that their resolution by this Court is important to the administration of the Federal Food, Drug, and Cosmetic Act of 1938, as amended. Accordingly, we agree that the Court should grant certiorari on the issues raised by the cross-petition, although, as indicated briefly below, we believe that Hynson's view of the proper resolution of these issues is erroneous, that Lutrexin is subject to the efficacy and "substantial evidence" requirements of the Act, and that there were no factual issues requiring resolution in an evidentiary hearing prior to withdrawal of Lutrexin's NDA.

1. Throughout the proceedings below, Hynson has contended that Lutrexin is not subject to the efficacy requirements of the 1962 amendments because it was generally recognized as safe at the time those amend-

ments went into effect and was therefore entitled to the exemption granted by Section 107(c)(4) from the efficacy requirements. Question 4 in the cross-petition (Pet. 3, 14–17) presents this issue. The court of appeals rejected this contention, concluding that since the NDA for Lutrexin, which was granted in 1953, had never been withdrawn, the drug was "covered by an effective application" within the meaning of Section 107(c)(4)(C) and therefore ineligible for the exemption (Pet. App. 23a–24a).[1] We agree with that holding. Indeed, Hynson's view that general recognition of safety by 1962 provides exemption would render clause (C) (set forth at Pet. App. 9a) meaningless and redundant. That clause has meaning only if, as the court below held, NDA's are "effective," for purposes of the statute, unless withdrawn, irrespective of any general recognition of the drug's safety that may have come about between the time of the NDA's effectiveness and the effective date of the 1962 amendments.

If this Court were to agree with Hynson's view of this issue, it would then be necessary, in administering the 1962 amendments, to determine the applicability of the efficacy requirements in the first instance by inquiring into a drug product's recognition for safety as of 1962, which would entail a major change from NDA withdrawal procedures now being pursued.

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[1] In reaching this conclusion, the court of appeals cited its decision in *USV Pharmaceutical Corp.* v. *Richardson* (Pet. App. 45a–54a), in which it discussed this issue at somewhat greater length. USV has petitioned for a writ of certiorari to review that decision (No. 72–666).

Additionally, the question is important because, should Hynson's view prevail, the impact of the efficacy requirements, as applied to drugs for which NDA's were filed prior to 1962, would be seriously constricted; thus, the issue is fundamental to establishing the reach of the 1962 amendments.

2. Question 3 presented by the cross-petition (Pet. 3, 17–20) raises a closely related legal question regarding the power of FDA to withdraw approval of an NDA in light of Section 107(c)(2). Relying upon the same basic contention that the NDA ceased to be "effective" when the drug achieved general recognition of safety, Hynson argues that the NDA for such a drug should not be "deemed * * * to be an application 'approved' by the Secretary * * *" and should therefore not be subject to administrative withdrawal of NDA approval under the efficacy requirements of Section 505(e)(3) (see Pet. 17–18). The factual issue presented, if Hynson's reading of the statute is correct, is identical to that presented under Hynson's interpretation of Section 107(c)(4), discussed above—was the drug generally recognized as safe at the time the 1962 amendments went into effect? The impact of a resolution of this question favorable to Hynson would also be similar, both in terms of the effective reach of the 1962 amendments and in terms of the manner of their administration.[2]

[2] It is true, as Hynson concedes, that the argument predicated on Section 107(c)(2), in contrast to that based on 107(c)(4), would not wholly eliminate the Act's efficacy requirements—it would eliminate effective administrative remedies but would leave the possibility of recourse to judicial remedies. As a

In our view, Hynson's strained interpretation of Section 107(c)(2) is incorrect. The obvious purpose of that provision was quite simple. Congress declared in that provision that previously issued NDA's were "deemed approved" because the 1962 amendments had changed the procedure whereby NDA's became operative. Prior to 1962, applications automatically became effective after the passage of a period of time following their filing, unless disapproved; thus, no formal approval was ever issued. The 1962 amendments, however, imposed an affirmative requirement of approval. Since previous NDA's had not been administratively "approved" but had simply become "effective" automatically, it was necessary for Congress to provide that all NDA's "effective" on the date of the amendments were deemed "approved" in order to make it clear that they were subject to the new "effectiveness" standards of the Act. Thus, far from insulating drugs for which NDA's had been filed under the old safety criteria, Section 107(c)(2) evidences the intent of Congress to insure that such drugs would be subject to the "effectiveness" requirement.

3. Question 2 presented by the cross-petition (Pet. 3, 13-14) apparently is intended to raise another related, and also important, issue. This is Hynson's con-

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practical matter, however, the effect would be nearly the same, since FDA does not have the resources to pursue judicial relief against the hundreds of drugs that might fall in the category claimed for Lutrexin of insulation from NDA withdrawal proceedings. Moreover, it is not clear whether "substantial evidence" of effectiveness—the statutory criterion for NDA withdrawals—would be required in defense against a seizure action or other judicial remedy.

tention that it should be entitled to show, at the time FDA is considering withdrawal of a previously issued NDA, that the agency is without jurisdiction to act because the drug has ceased to be a new drug, having become generally recognized as both safe and effective (the criteria under the amended Act). This argument (which was not discussed by the court of appeals) is, in essence, an attempt to avoid the impact of the "substantial evidence" requirement adopted by Congress in Sections 505 (d) and (e) of the Act (Pet. App. 3a-6a) as the standard for determinations of efficacy. In other words, Hynson seeks to be able to rely on the kind of evidence it submitted to FDA to establish "general recognition" of efficacy, thereby, in its view, depriving the agency of the power to move against its drug even though there is no "substantial evidence" of efficacy.

Almost any drug that has been on the market since 1962 or earlier, and that has been sufficiently successful economically that the manufacturer desires to resist its removal from the market for ineffectiveness, is likely to have some sort of "recognition" of safety and effectiveness among some members of the medical profession. The manufacturer of such a product, therefore, could produce testimonials in its support sufficient, under Hynson's contention, to raise an issue requiring a hearing even in the absence of any evidence of the kind defined by Congress as "substantial evidence." The result of acceptance of Hynson's position on this issue thus would be effectively to read

the "substantial evidence" requirement out of the statute, at least with respect to withdrawals, and to allow manufacturers having no "adequate and well controlled investigations" substantiating the effectiveness of their products to avoid the NDA procedure. We do not agree that the clear intent of Congress can be so readily subverted; in our view, there can be no general recognition of safety and effectiveness in the absence of "substantial evidence" of effectiveness.

4. Question 1 presented by the cross-petition (Pet. 3, 9–12) concerns the jurisdiction of FDA to determine whether Lutrexin is exempt from withdrawal of its NDA under any of the threshold jurisdictional contentions presented by questions 2 through 4 of the cross-petition. In other words, if this Court should agree with Hynson on its claims that it is entitled as a matter of law to prove that Lutrexin is exempt from the Act because generally recognized as safe at the time the 1962 amendments went into effect (questions 3 and 4 of the cross-petition) or because generally recognized as safe and effective today (question 2), the Court would also have to determine whether, on remand, the agency has the jurisdiction to resolve the factual questions upon which the availability of any such exemption rests.

Under the ruling of the court of appeals in *Bentex Pharmaceuticals, Inc.* v. *Richardson* (Pet. App. 29a–44a), the agency apparently would not have such jurisdiction, and the questions would have to be resolved in the district court. The government has peti-

tioned for a writ of certiorari to review the *Bentex* decision (No. 72-555), and we agree with Hynson that the agency should and does have jurisdiction to determine such questions. (Of course, we do not agree that any such jurisdictional questions are present in the case of Lutrexin, since, as indicated above, we believe that the contentions advanced by Hynson in its cross-petition as grounds for exemption from the Act's efficacy requirement are lacking in legal merit.)

5. The questions presented in the cross-petition reflect recurring contentions made by manufacturers seeking to avoid application of the efficacy requirements of the 1962 amendments (and the "substantial evidence" standard embodied therein) to their products. In order to avoid fragmented litigation of these questions in federal courts all over the country during the next several years, we believe it is important for this Court to provide an authoritative interpretation of the efficacy provisions contained in the 1962 amendments. This case, together with *Bentex*,[3] provides a suitable framework for resolution of these complex, important, and interrelated problems.

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[3] Similar issues are also presented in two additional cases now pending on petitions for writs of certiorari. *Ciba Corporation* v. *Richardson*, No. 72-528; *USV Pharmaceutical Corp.* v. *Richardson*, No. 72-666.

CONCLUSION

For the reasons stated, the cross-petition for a writ of certiorari, as well as the government's petition, should be granted.

Respectfully submitted.

ERWIN N. GRISWOLD,
Solicitor General.

THOMAS E. KAUPER,
Assistant Attorney General.
PETER BARTON HUTT,

PETER BARTON HUTT,
Assistant General Counsel,
Food, Drugs, and Product Safety Division,
Department of Health, Education, and Welfare.

NOVEMBER 1972.

U.S. GOVERNMENT PRINTING OFFICE: 1973

In the Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-528

CIBA CORPORATION, PETITIONER

v.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND DR. CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

MEMORANDUM FOR THE RESPONDENTS

1. Petitioner manufactures a drug product, Ritonic Capsules, for which it filed a New Drug Application (NDA) that became effective in 1958. Subsequent to the passage of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act of 1938, which authorized the Food and Drug Administration (FDA) to withdraw approval of the NDAs of certain drugs if the manufacturer could not establish their effectiveness, FDA commenced proceedings to withdraw approval of Ritonic Capsules' NDA. These proceedings culminated in a withdrawal of the NDA, and Ciba petitioned for review of that action, under Section

489-351—72

505(h) of the Act, to the Court of Appeals for the Second Circuit, which affirmed the action of FDA. *Ciba-Geigy Corp.* v. *Richardson*, 446 F. 2d 466. Supreme Court review of that decision was not sought. Petitioner also filed the present declaratory judgment action in the District Court for the District of New Jersey, seeking a declaration that its product was not a "new drug" and could therefore be freely marketed notwithstanding the withdrawal of the NDA. The district court declined, in its discretion, to entertain the action, and the court of appeals affirmed (Pet. App. 9a–10a).

2. In the declaratory judgment action, petitioner contended that its drug was marketable under two theories: (1) that it was exempt from the efficacy requirements of the 1962 amendments under the terms of the grandfather clause contained therein (P.L. 87-781, Section 107(c)(4), 76 Stat. 789, note following 21 U.S.C. 321 (1970 ed.)) because it had come to be generally recognized as safe by 1962; (2) that it does not now fall within the statutory definition of a "new drug" requiring an approved NDA because it is presently generally recognized as safe and effective.[1] On appeal, petitioner presented the question whether the district court had jurisdiction to entertain the

[1] Section 201(p) of the Act defines a "new drug" (for purposes material here) as: "Any drug * * * the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof * * *." 21 U.S.C. 321(p)(1).

declaratory judgment action and whether dismissal of the action was a proper exercise of the court's discretion. In support of its appeal petitioner urged, as it does in this Court, that FDA is without jurisdiction to determine the questions presented in the declaratory judgment proceeding, and that they were therefore appropriately presented for resolution by the district court.

3. The court of appeals held that FDA had jurisdiction to decide the threshold question whether the product subject to NDA withdrawal proceedings is a "new drug" and that such a determination could have been reviewed in the direct judicial review proceedings in the Second Circuit. Since the court was of the view that petitioner's contentions should have been raised before the agency and on direct judicial review, it concluded, without expressly reaching the issue of the district court's jurisdiction to entertain the declaratory judgment action, that it "is neither necessary nor appropriate that the District Court for the District of New Jersey entertain a separate suit by the loser in the administrative proceeding and in the direct appeal therefrom for a redetermination of the same question" (Pet. App. 10a).

4. We believe that the court of appeals was correct in holding that petitioner should have submitted its contentions to FDA in the administrative proceedings and should not now be afforded the opportunity for fresh litigation of these issues in the district court. We agree with petitioner, however, that the decision of the court below on the scope of the FDA's authority is in conflict with the decision of the Fourth Cir-

cuit in *Bentex Pharmaceuticals, Inc.* v. *Richardson*, 463 F. 2d 363, from which the government has petitioned for a writ of certiorari, *Elliot Richardson, et al.* v. *Bentex Pharmaceuticals, Inc.*, No. 72-555.

Arguably, there is a distinction between the instant case and *Bentex*, since the latter involves drug products for which no NDA was ever effective, and therefore no NDA withdrawal proceedings were undertaken by the agency.[2] The reasoning of the Court of Appeals for the Fourth Circuit in *Bentex*, however, was based on the premise that FDA lacks jurisdiction to determine whether a drug product is subject to the Act, contrary to the conclusion of the court of appeals in the instant case. And in terms of the exercise of equitable discretion in deciding whether to entertain a declaratory judgment action, both cases raise the important question whether the agency or the courts should make the initial determination.[3]

---

[2] Bentex and the other manufacturers joining as plaintiffs in the declaratory judgment action in the *Bentex* case manufactured drug products similar in formulation to a product for which another firm held an NDA. When the NDA was withdrawn, FDA took the position that the action covered the plaintiffs' products as well, and thus effectuated a withdrawal of their marketing authorization. This position was challenged in the declaratory judgment action, which presented the threshold question whether the factual and legal issues raised by, or the courts. The district court, in the exercise of its discretion, stayed the court proceedings in order to permit the agency to make the initial determination. The court of appeals held that only the courts had authority to determine these questions, and therefore reversed the decision of the district court.

[3] While the circuits are in conflict on the jurisdictional issue, it appears that the Court of Appeals for the Fourth Circuit, which would have reached the merits of petitioner's claims, would have ruled adversely to petitioner on the merits. See

the controversy should be initially determined by the agency

Because of the conflict between the circuits, and because the petition is one of several now pending that present related questions which are important to effective administration of the Food, Drug, and Cosmetic Act,[4] we do not oppose the granting of the petition for a writ of certiorari in this case.

Respectfully submitted.

ERWIN N. GRISWOLD,
Solicitor General.

PETER BARTON HUTT,
Assistant General Counsel,
Food, Drugs and Product Safety Division,
Department of Health, Education, and Welfare.

NOVEMBER 1972.

USV Pharmaceutical Corp. v. *Richardson*, 461 F. 2d 223, 226–228, *Westcott and Dunning, Inc.* v. *Richardson*, 461 F. 2d 215, 219, petitions for writs of certiorari pending, Nos. 72–394 and 72–414. The views of the Fourth Circuit on the merits, of course, do not eliminate the conflict on the jurisdictional issue.

[4] In addition to the government's petition in *Bentex*, and CIBA's petition in this case, there are also pending a petition by the government in *Richardson* v. *Hynson, Westcott & Dunning, Incorporated*, No. 72–394; a cross-petition in the same case, *Hynson Westcott & Dunning, Incorporated* v. *Richardson*, No. 72–414, which the government has urged the Court to grant; and a petition in *USV Pharmaceuticals Corp.* v. *Richardson*, No. 72–666.

petition for writ of certiorari pending, No. 72-666; Hynson,

U.S. GOVERNMENT PRINTING OFFICE: 1972

COPY

72-555
No.

SUPREME COURT, U. S.
FILED
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MICHAEL RODAK, JR., CLERK

IN THE

Supreme Court of The United States

OCTOBER TERM, 1972

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

Petitioners

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

Respondents.

RESPONDENTS' BRIEF TO PETITION FOR A WRIT OF CERTIORARI

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS,

Petitioners

v.

BENTEX PHARMACEUTICALS, INC., ET AL,

Respondents.

RESPONDENTS' BRIEF TO PETITION FOR A WRIT OF CERTIORARI

COUNTER STATEMENT

The petitioner's statement implies that the jurisdiction of the FDA administratively to adjudicate whether a drug requires an approved new drug application in order to be marketed is related to the issue of whether it is a copy of a drug which has already received such approval.

Under the decision below this relationship is irrelevant. In the present case this relationship is irrelevent, regardless of the theory of law required, since the respondents' products are not "me-too" drugs.

This appeal has arisen prior to the reception of evidence and testimony. Thus the "me-too" status of the respondent's drugs has not been developed in the record. However the fact that the respondent's drugs are not "me-too" drugs is evident.

The Petition (footnote 8, page 6) states that the products subject to NDA withdrawal proceedings were "Nicozol with Reserpine" and "Geroniozol injectible."

The respondent's products differ from the two products for which NDAs were outstanding in that they do not contain reserpine and are orally administered rather than injectibles.[1]

The respondents' products are not copies of Nicozol with Reserpine and Geronizol injectible. This position of the respondents was noted both by the District Court (Petition, page 20a) and the Court of Appeals (Petition, footnote 18, page 9a and 10a), and that the NDA'd products were copies of the respondent's formulation rather than the converse.

The clear inference arises that in fact the two NDA'd products are inferior derivations of the respondents' "pioneer" formulation.

The present case is not an appropriate vehicle for consideration of issues involving "me-too" drugs.

ARGUMENT AGAINST GRANTING THE WRIT

The opinion of the Court below is a full and clear analysis of the Act and supporting authorities. It would be redundant in this argument to repeat the exposition of the Food, Drug and Cosmetic Act contained in that opinion.

The opinion, which is of notable logic and scholarship, arises out of three cases involving the same jurisdictional issue here appealed. These were the present case, *USV Pharmaceutical Corp. v. Richardson,* (461 F. 2d 223) *Hynson, Wescott and Dunning, Inc. v. Richardson,* (Fourth Circuit, No. 72-394, Petition for Certiorari filed September 7, 1972).

In the present case the Court considered the FDA's jurisdiction to pass on the status of drugs which have had no NDA. In the *USV* case the Court considered the jurisdiction of the FDA to pass upon the status of drugs in which an NDA existed. In the *Hynson* case both the manufacturer who held

[1] A preparation of an old drug for administration by novel means requires an approved new drug application. The manner in which a drug is administered has an important bearing on its safety and efficacy.

an NDA, and the FDA, had treated the case as though the FDA had jurisdiction to determine the old drug-new drug status of the product involved, and the Court ruled on the consequences of their position.

These three cases, fully argued and considered, provided the Court below with an invaluable insight into the structure of the Food, Drug and Cosmetic Act. They gave the Court the opportunity to understand the provisions of the Act as an integral whole.

The case of *Ciba-Geigy Corporation v. Richardson* (No. A-249, Third Circuit, Petition for Certiorari being filed on or about October 2, 1972) conflicts with the decision in the present case.

The *Ciba-Geigy* decision is of note primarily for its brevity and for the absence of any cited authority for its conclusions. Its fallaciousness is immediately revealed in the opinion of the Fourth Circuit. The *Bentex* case was decided just prior to the decision of the Third Circuit. Nothing indicates that the Third Circuit considered the analysis contained in the present decision.

The *Ciba-Geigy* case does not constitute a conflict between Courts of Appeal of sufficient import to warrant a review by the United States Supreme Court.

• • • •

The Courts have not agreed with the petitioner's statement that application of the definition of a "new drug" turns on "the determination of complex medical and pharmacological questions." (Petition, page 12).

Whether a drug is a "new drug", i.e. not generally recognized among qualified experts as safe and effective, is a question which merely requires the Court to determine the reputation of the drug among qualified experts.

> In such a case as this, the Court does not decide whether the drug is safe and effective; the Court lacks the necessary expertise to make that decision . . . . The question which this Court must decide in this case, with respect to each variation, is whether the

> government has shown by preponderance of the evidence that the 'drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested on the labeling thereof.' U. S. v. . . . . Quickover, 274 F. Supp. 443 (Md. 1967).
>
> Under the statute the question is not whether in point of fact Line Away is unsafe or ineffective. It is whether qualified experts generally recognize Line Away to be unsafe and ineffective for its recommended uses. U. S. v. 36 boxes . . . Line Away, 284 F. Supp. 107 (Del. 1968).

This question is no more difficult than the determination, based on expert testimony, of the relationship of an injury to a disability in a Workman's Compensation case.

The old drug-new drug issue has been commonly determined by summary judgment, based upon affidavits that qualified experts do or do not generally recognize a drug to be safe and effective for its intended uses.

The petitioner concedes that it has no power by administrative action to compel a manufacturer to remove a drug from the market (Petition, page 17).

This can be compelled only by action in a District Court.

The volume of cases of this nature is small. A few cases only are reported each year. The present decision will not add to the case load of the Courts, for the Commissioner has not heretofore exercised the jurisdiction which he now asserts.

As observed by the Court below:

> It is not without significance that, as far as the official reports reflect, the Secretary has never attempted directly to exercise such jurisdiction. The only occasions on which he has sought to assert such jurisdiction has been as an element in his defense to a declaratory judgment action.
> (Petition, pages 12a and 13a).

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted,

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October 1972

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In the Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-666

USV PHARMACEUTICAL CORPORATION, PETITIONER

v.

ELLIOT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

MEMORANDUM FOR THE RESPONDENTS

This petition for a writ of certiorari is the most recent in a series of petitions filed both by the government and by drug manufacturers concerning the interpretation of, and the procedures to be followed under, the drug effectiveness provisions of the 1962 Amendments to the Federal Food, Drug, and Cosmetic Act of 1938 (76 Stat. 780–796).[1] Those amendments sup-

[1] Other petitions are *Elliot L. Richardson, et al.* v. *Hynson, Westcott and Dunning, Incorporated*, No. 72-394; *Hynson, Westcott & Dunning, Incorporated* v. *Elliot L. Richardson, et*

plemented the basic Act's requirement that drugs available to the public be safe by adding the further requirement that they be effective for their intended uses. See Sections 505(a) and 201(p)(1) of the Act (21 U.S.C. 355(a) and 321(p)(1)). The Act now prohibits the interstate shipment of any "new drug" unless there is a new drug application ("NDA") approved by the Secretary of Health, Education, and Welfare [2] effective with respect to such drug.[3]

Congress also provided in Section 107(c)(4) of the 1962 amendments a "grandfather" exemption from the new effectiveness requirements. It made the exemption available to a drug which, on the day prior

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al., No. 72–414 (cross-petition); *CIBA Corporation* v. *Elliot L. Richardson, et al.*, No. 72–528; and *Elliot L. Richardson, et al.* v. *Bentex Pharmaceuticals, Inc., et al.*, No. 72–555.

[2] Under both the basic 1938 Act and the Act as amended in 1962, the Secretary has delegated his authority to the Commissioner of the Food and Drug Administration ("FDA").

[3] Congress altered the manner in which NDA's become effective. Under the basic 1938 Act, an NDA automatically became effective sixty days after filing (or one hundred and eighty days, if postponed by FDA) unless in that time FDA issued an order refusing to permit the application to become effective. See 52 Stat. 1052. As amended in 1962, the Act now requires affirmative approval of FDA before an NDA may become effective. See Sections 505 (b), (c) and (d) of the Act (21 U.S.C. 355 (b), (c) and (d)).

At the same time, Congress declared that "[a]n application filed pursuant to section 505(b) of the basic Act which was 'effective' within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application 'approved' by the Secretary within the meaning of the basic Act as amended by this Act." P.L. 87–781, Section 107(c)(2), 76 Stat. 788, note following 21 U.S.C. 321 (1970 ed.).

to enactment of the amendments (October 9, 1962), (1) was commercially sold or used in the United States, (2) was not a "new drug" as defined by Section 201(p) of the basic 1938 Act, and (3) was not covered by an effective application under Section 505 of that Act.[4] This case involves the interpretation of this "grandfather" exemption.

1. Petitioner sells a line of citrus bioflavonoid drugs.[5] In 1956 and 1957 it had filed with FDA three NDA's covering seven of these drugs. In accordance with the terms of Section 505(c) of the 1938 Act (52 Stat. 1052), these NDA's automatically became effective after sixty days, FDA having issued no order refusing to permit them to become effective. USV also marketed two other drugs prior to 1962, similar in formula and labeling to the original seven, for which it had never filed an NDA (Pet. App. 2a, 6a). Such copies of earlier drugs are known as "me-too" drugs.

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[4] Section 107(c)(4) reads: "In the case of any drug which, on the first day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day." P.L. 87-781, Section 107(c)(4), 76 Stat. 789, note following 21 U.S.C. 321 (1970 ed.).

Sections 201 and 505 of the basic 1938 Act are found at 52 Stat. 1041-1042, 1052-1053.

[5] USV asserts that its citrus bioflavonoids are effective in the control of abnormal capillary permeability and fragility (Pet. 3).

In 1968, following reports by the National Academy of Science-National Research Council finding bioflavonoids to be ineffective (Pet. App. 39a–41a), FDA began proceedings under Section 505(e) of the amended Act (21 U.S.C. 355(e)) to withdraw approval of the NDA's for USV's bioflavonoids on the ground of ineffectiveness (Pet. App. 41a).[6] USV then sued in the district court for a declaratory judgment that its drugs are entitled to the exemption provided in Section 107(c)(4).

The district court ruled that it, and not FDA, had jurisdiction to decide the exemption question (Pet. App. 14a). It then held that all nine of the drugs were exempt: the "me-too" drugs because they were never covered by effective NDA's; the other seven drugs because USV had withdrawn their NDA's prior to October 9, 1962 (Pet. App. 14a–15a).[7] On the government's appeal the court of appeals, while agreeing that

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[6] The administrative proceedings culminated in an order issued October 15, 1970, in which the Commissioner withdrew approval of USV's NDA's for lack of substantial evidence of effectiveness (Pet. App. 46a). On review, the United States Court of Appeals for the District of Columbia Circuit reversed the Commissioner for failure to meet the requirements of administrative due process. *USV Pharmaceutical Corporation* v. *Secretary of Health, Education & Welfare and Commissioner of Food & Drugs*, C.A.D.C., No. 24,900 (August 12, 1972) (Pet. App. 36a–49a). The government has decided not to seek review of that decision. That decision does not, however, moot the issues in the present case, since FDA's withdrawal proceedings are continuing on remand.

[7] The district court found that USV's drugs were commercially used and sold in the United States on October 9, 1962. It also found that on that date all of the drugs were generally recognized as safe and hence were not new drugs as that term was defined in Section 201(p) of the basic Act then in force (Pet. App. 14a–15a).

the district court alone had jurisdiction,[*] reversed on the merits and held that none of the drugs were entitled to the exemption (Pet. App. 1a–10a). As to the seven drugs for which NDA's had been filed, the court stated that USV was without authority to withdraw an NDA once it was effective. Therefore, even though the drugs were generally recognized as safe on October 9, 1962, they nevertheless were "covered by an effective application" within the meaning of Section 107(c)(4)(C) and were thus not exempt from the drug effectiveness requirements of the 1962 amendments (Pet. App. 4a–6a). As to the two me-too drugs, the court held that, even if it be assumed that the me-toos of other manufacturers competing with USV's bioflavonoids would be exempt, USV's me-toos were not exempt because the NDA's covering its pioneer drugs, which are personal to USV, covered all of its products similar in formula and labeling (Pet. App. 6a–10a).

2. USV's petition for a writ of certiorari presents questions concerning the applicability of Section 107 (c)(4)'s exemption from the effectiveness requirements of the Act. While we do not agree with petitioner's formulation of the questions, we believe that, in light of the congressional purpose to protect the public from ineffective drugs, the interpretation of the grandfather exemption presents important issues which should be considered on this record. These issues are

[*] The court on this point cited its opinion in *Bentex Pharmaceuticals, Inc.* v. *Richardson*, 463 F.2d 363 (C.A. 4) (Pet. App. 20a–35a). The government has filed a petition for a writ of certiorari in that case: *Elliot L. Richardson, et al.* v. *Bentex Pharmaceuticals, Inc. et al.*, No. 72–555.

(1) whether a drug for which an NDA was issued prior to 1962 and never suspended by governmental action is "covered by an effective [NDA]" and therefore not exempted, and (2) whether me-too copies of such drugs are covered by the NDA of the pioneer drugs for purposes of Section 107(c)(4). These questions are important, because there are many NDA drugs and me-too drugs for which manufacturers can make the same claims to exemption that USV makes here. We believe that, in its present posture, this case fairly presents these issues and that their resolution by this Court is important to administration of the Act. Thus we agree that the Court should grant the petition for a writ of certiorari, although, for the reasons briefly stated below, we believe that none of USV's drugs is entitled to exemption.[9]

A. Petitioner's first contention is that, because its drugs were found by the courts below to have been

[9] We note that the court of appeals, on the strength of its opinion in *Bentex*, *supra*, also held that the courts alone have jurisdiction to decide whether a drug is entitled to the exemption (Pet. App. 2a). We have filed a petition for review of the *Bentex* decision (*Elliot L. Richardson, et al.* v. *Bentex Pharmaceuticals, Inc., et al.*, No. 72–555) in which we not only contend that FDA does have jurisdiction to decide whether a drug is a new drug, but also indicate that where technical questions relating to agency expertise are involved, the primary jurisdiction doctrine may oblige courts to defer to FDA. Pet. No. 72–555, *supra*, at p. 18, n. 15. We adhere to that view. But since, after a full district court trial, there are now no disputed issues of fact in the present case, and since there remain only important and generally applicable issues of statutory construction on which the agency's views are being presented by the government, we believe it would be proper for this Court to decide the issues presented by USV's petition.

generally recognized as safe prior to October 9, 1962, and because FDA was found to have acquiesced in USV's cessation of adherence to the labeling and data submission procedures required for NDA products, the drugs had ceased to be new drugs under the basic Act and were no longer "covered by an effective application" as of that date (Pet. 14–18). The court of appeals rejected this argument on the grounds that nothing in the statute gave a manufacturer the right to withdraw an effective NDA, and that to treat NDA drugs as new drugs exempt from the Act because they are generally recognized as safe would make meaningless surplusage of Section 107(c)(4)'s further requirement that, prior to the enactment date, the product not be "covered by an effective application."[10]

The court of appeals' construction accords with the congressional purpose as well as with the statutory language. Section 107(c)(4) limits exemptions from the efficacy requirement to drugs which, as of October 9, 1962, were not "new drugs" within the meaning of Section 201(p) of the 1938 Act (Section 107(c)(4)(B)) *and* were not covered by an effective NDA (Section 107(c)(4)(C)). The requirements are conjunctive, not alternative. Thus clause (C) presupposes that the drugs to which it applies were, in accord with clause (B), not new drugs. The argument

[10] The same contention was also rejected by the Fourth Circuit in *Hynson, Westcott & Dunning, Inc.* v. *Richardson*, 461 F. 2d 215, and Hynson has raised the issue before this Court in its cross-petition for a writ of certiorari (No. 72–414). The government has acquiesced in the granting of Hynson's cross-petition in No. 72–414.

that general recognition of safety, and thus the loss of new drug status, by 1962 entitled a drug to a Section 107(c)(4) exemption would render clause (C) of the exemption section meaningless and redundant. Had Congress intended to adopt USV's view, it would have provided exemption for any drug which "was not a new drug" under the basic Act, "and *therefore* was not covered by an effective application."

Nor is USV's argument of greater merit when combined with evidence that USV, with the acquiescence of FDA, ceased to comply with certain procedures required of effective NDA's. As the court of appeals rightly observed, nothing in the basic 1938 Act authorizes a manufacturer to withdraw an effective NDA, either directly or indirectly. Indeed, prior to the 1962 amendments, FDA itself had no authority to withdraw an NDA. It could only suspend the effectiveness of an application, and the 1938 Act carefully prescribed both the substantive grounds for suspension and the procedural rights which the government had to afford the party affected. See 52 Stat. 1053. In view of the specificity with which Congress delimited the powers of FDA to suspend the effectiveness of an NDA, petitioner's admittedly inferential attempt to add to the statutory scheme a new means for rendering NDA's ineffective (Pet. 17) is without foundation.

B. Petitioner's second contention is that the court of appeals erred in holding that USV's me-too drugs were not exempt under Section 107(c)(4), while indicating that such me-too drugs, if produced by another manufacturer, would be exempt (Pet. 18–22). The

court of appeals assumed, *arguendo*, that as a general rule me-too drugs are entitled to exemption. This conclusion was based on its view that, under Section 505, NDA's are personal to the manufacturer and specific to the drug covered, a view reinforced by FDA's pre-1962 practice. However, the court held that USV's me-too drugs, being similar to other USV products covered by effective NDA's, are not exempt because the personal character of the NDA extends its coverage to all similar products of the manufacturer (Pet. App. 8a–10a).

We believe that the court of appeals reached the right result, but for the wrong reason. The purpose of Congress in passing the 1962 drug effectiveness amendments was to insure that drugs marketed to the American public are effective as well as safe. Thus, even though a drug was covered by an NDA issued prior to October 10, 1962, the amendments required that it meet the new standard of effectiveness. This congressional intent to protect the public against ineffective drugs would be frustrated in substantial measure if the large body of me-too drugs, similar in composition and labeling to NDA drugs, could be sold to the public regardless of their effectiveness.[11]

It is in light of this important statutory purpose that the coverage language of Section 107(c)(4)

[11] Moreover, such a result would create competitive inequities among drug manufacturers by requiring the holder of an NDA to show the effectiveness of its product while leaving the manufacturer of the me-too free to market an imitation of the drug even if it is ineffective. Such an unfair result should not lightly be attributed to Congress.

should be read. Section 107(c)(4) provides exemption for a drug "not covered by an effective application under Section 505" of the basic 1938 Act. It is our position that me-too drugs are "covered" by the effective NDA of the pioneer, whether the me-toos are made by the manufacturer of the pioneer drug or by a competitor, because the me-toos are basically the same pharmacologically as the NDA drugs, and because issuance of the pioneer's NDA normally provided the predicate for lawful marketing of the copies.

Although both the petitioner and the court of appeals maintain that NDA's were "personal" to each manufacturer of the drug under Section 505 of the 1938 Act, the statute's provisions suggested a broader, generic coverage for NDA's. Section 505(a) provided that "[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an application filed pursuant to subsection (b) is effective with respect to such drug." 52 Stat. 1052. And Section 505(b), in its list of items of information to be supplied to FDA, contained items which looked to the safety of the drug as a generic article, in addition to "personal" information on the methods, facilities and controls which a particular company would use in its manufacture, processing and packaging.[12] The generic factors applied to a drug whether it was made by USV or by a competitor; in other words, under the 1938 Act, either citrus bioflavonoids

[12] Compare Section 505(b)(1)–(3) with Section 505(b)(4). 52 Stat. 1052.

of a particular pharmacological composition and intended use were safe or they were not safe. When FDA permitted the original NDA's to become effective, therefore, the NDA's presumptively established (subject to possible subsequent re-evaluation and suspension) that the formulation and use covered was marketable as a general class of product.

It is true, as petitioner and the court of appeals point out (Pet. 19–21; Pet. App. 8a–9a), that respondents' present position represents a change from that taken for many years prior to 1962. Enactment of the 1962 amendments, however, necessitated reconsideration of the distinction formerly made by FDA between the personal and generic attributes of an NDA. In order to carry out the statutory purpose of insuring the effectiveness of drugs, FDA properly recognized that NDA's could be treated as generic in matters susceptible of such treatment. An NDA thus could rightly be said, as to generic matters (as distinguished from particularized matters relating to conditions of production, etc.), to be "effective" under Section 505 not only for the particular drugs but for all others similar in composition and use. Accordingly, USV's effective NDA's covered not only USV's me-too drugs, but any competitor's me-toos as well.[13]

[13] If, however, the Court should reject respondents' interpretation of the exemption and read NDA's as being personal to the manufacturer and the drug, then we agree with petitioner that the distinction drawn by the court of appeals between USV's me-toos and those of its competitors is discriminatory and not supportable.

3. USV's petition appears to be the last in the current group of petitions raising questions involving the interpretation and administration of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act. All told, four decisions of the courts of appeals have generated five petitions for certiorari stating nine questions for resolution by this Court. The government has filed two of these petitions (*Hynson*, No. 72-394; and *Bentex*, No. 72-555) and has recommended the granting of certiorari in the other three (*Hynson* (cross-petition), No. 72-414; *CIBA*, No. 72-528; and the instant case, *USV*, No. 72-666).

While the Court may, if it decides to grant certiorari in any or all of the cases, wish to hear them in the normal manner, we believe that the degree of interrelation among the cases and the extent to which they present overlapping issues warrant consideration of an alternative approach designed to avoid unnecessary duplication of arguments and to focus the issues for resolution by the Court. Accordingly, we respectfully offer to the Court and the other parties the following suggestions for the briefing and argument of these cases.

In our view, the nine questions presented by the pending petitions can fairly be grouped into three general questions, which are logically susceptible of separate briefing and argument: (a) whether particular categories of drug products are immune from the efficacy requirements of the 1962 amendments; (b) whether the resolution of certain factual issues inci-

dent to the determination of the lawfulness of marketing of a drug is exclusively within the jurisdiction of the courts; and (c) whether FDA may, in certain circumstances, properly decline to hold an evidentiary hearing under Section 505(e).

(a) *The "immunity" issues.* Questions 3 and 4 raised by the cross-petition in *Hynson* (No. 72–414) and question 1 presented by USV's petition in the instant case involve the interpretation of Section 107(c)(4) and the contention that drugs for which NDA's became effective between 1938 and 1962 are immune under that provision from the efficacy requirements of the 1962 amendments if they were generally recognized as safe by 1962. Question 2 presented by USV's petition in the instant case raises the question whether Section 107(c)(4) confers immunity from the efficacy requirements of the 1962 amendments upon ineffective me-too drugs when the NDA of the pioneer of which they are copies is withdrawn because of the absence of substantial evidence of the drug's effectiveness (this issue is also inherent in *Bentex,* although not necessary to the decision of the court of appeals because of its disposition of the jurisdictional issue). Question 2 presented by the cross-petition in *Hynson, supra,* involves the contention that a drug that is today "generally recognized" as safe and effective is immune from the requirement that it adduce "substantial evidence" of effectiveness.

We propose that Hynson and USV file opening briefs addressed to these "immunity" issues, and that the government file a brief in response on this group of

issues.[14] We suggest that the Court grant one and a half hours of oral argument on these issues.

(b) *The jurisdictional issues.* The government's petition in *Bentex* (No. 72–555) raises the issue whether the FDA had jurisdiction to determine initially whether a product is a "new drug" which must be administratively approved as safe and effective before it may be sold in commerce. The manufacturer's petition in *CIBA* (No. 72–528) raises the issue whether the federal district courts have exclusive jurisdiction to adjudicate the "new drug" status of a product, the manufacturer having failed to raise the issue in administrative proceedings for withdrawal of the drug's NDA and on direct judicial review of such proceedings. Both of these questions, together with question 1 presented by the cross-petition in *Hynson, supra,* raise fundamental issues concerning the jurisdiction of court and agency to resolve factual contentions upon which "immunity" claims may turn.

With respect to these jurisdictional issues, we propose that the government file an opening brief and that Bentex, CIBA, and Hynson file briefs in re-

[14] Since "immunity" claims underlie the declaratory judgment actions brought by the *Bentex* respondents and by CIBA, those parties may wish to brief the "immunity" issues also, and the government would have no objection to their doing so.

sponse. We suggest that the Court grant one hour of oral argument on these issues.

(c) *The hearing issue.* The government's petition in *Hynson* (No. 72–394) challenges the order of the court of appeals requiring the grant of an evidentiary hearing to Hynson, in connection with the withdrawal of an NDA under Section 505(e), in the absence of submission by Hynson of "substantial evidence" of effectiveness, consisting of adequate and well-controlled clinical investigations, in support of its request for a hearing. We propose that this case be handled in the normal manner.

The foregoing is not intended to suggest that the three general topics delineated above are unrelated to one another. On the contrary, we believe they are interrelated, but that the precise nature of the relationship is dependent in part upon the manner in which the various questions presented by these cases are answered. On balance, however, we believe that the topical division suggested herein may provide a useful framework for analysis and resolution of the complex and interrelated issues raised by the pending petitions.

4. Copies of this Memorandum are also being served upon Bentex, CIBA, and Hynson so that they may have an opportunity to respond to our suggestions concerning the procedure for briefing and argument of these cases.

CONCLUSION

For the reasons stated, the present petition for a writ of certiorari should be granted.

Respectfully submitted.

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DECEMBER 1972.

U S GOVERNMENT PRINTING OFFICE: 1972

AMICUS CURIAE BRIEF

OCT 31 1972

No. 72-394

IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

ELLIOT RICHARDSON, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners,

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

MOTION FOR LEAVE TO FILE BRIEF AMICI CURIAE IN SUPPORT OF PETITION OF THE UNITED STATES FOR A WRIT OF CERTIORARI AND BRIEF AS AMICI CURIAE IN SUPPORT OF PETITION OF THE UNITED STATES FOR A WRIT OF CERTIORARI ON BEHALF OF THE AMERICAN PUBLIC HEALTH ASSOCIATION AND NATIONAL COUNCIL OF SENIOR CITIZENS

Supreme Court, U.S.
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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-394

ELLIOT RICHARDSON, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners,

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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MOTION FOR LEAVE TO FILE BRIEF AMICI CURIAE IN SUPPORT OF PETITION OF THE UNITED STATES FOR A WRIT OF CERTIORARI ON BEHALF OF THE AMERICAN PUBLIC HEALTH ASSOCIATION AND NATIONAL COUNCIL OF SENIOR CITIZENS

The American Public Health Association and National Council of Senior Citizens hereby respectfully move for leave to file the attached brief *amici curiae* in support of the petition of the United States for a writ of certiorari in this case. The consent of the United States has been obtained and has been filed with the Clerk of this Court. The consent of the respondent was requested but denied.

The immediate interest of the American Public Health Association and National Council of Senior Citizens in this case arises from the fact that they have been successful plaintiffs in a recent court action against the Food and Drug Administration. The Food, Drug and Cosmetic Act requires the Food and Drug Administration to remove drugs marketed between 1938 and 1962 from the market if the FDA find that they lacked substantial evidence of effectiveness. The FDA has still not completed its review of most of those drugs 10 years later and therefore hundreds of drugs, which the National Academy of Sciences and the FDA itself have found to be ineffective, are still being sold. The district court, on October 11, 1972, directed the FDA to proceed "expeditiously" to withdraw drugs found to be ineffective and established specific deadlines for implementation of the determination. *American Public Health Ass'n* v. *Veneman*, No. 1847-70, District Court for the District of Columbia.[1]

As is described more fully in the attached brief in support of the petition of the United States for a writ of certiorari, the decision of the court of appeals in this case may seriously interfere with compliance by the Food and Drug Administration with the order of the district court in *American Public Health Ass'n* v. *Veneman*. The decision of the court of appeals will impose substantial additional burdens on the FDA which has already failed to enforce the 1962 amendments to the Food, Drug and Cosmetic Act. The American Public Health Association and National Council of Senior Citizens seek to file a brief supporting the petition of the United States to protect the order of the district court and, more broadly, the interest of the public in the enforcement of this extremely important statute.

The involvement of the American Public Health Association and National Council of Senior Citizens in *Ameri-*

[1] The opinion and order of the district court are included in the appendix below.

can *Public Health Ass'n* v. *Veneman* is the culmination of the long-standing concern of both organizations for protecting the public from the abuses of ineffective drugs. Formed in 1961, the National Council of Senior Citizens is a non-profit association of over 3,000 senior citizen groups from different states with a combined membership of over 3,000,000 elderly people. The purpose of the organization is to provide education and to act as a national clearinghouse on matters of interest to senior citizens. The interest of the elderly in drug effectiveness is a critical one. Of people 65 and older, over 85 percent are suffering from one or more chronic conditions and, as a result, elderly people use three times the amount of drugs as the average American citizen. This need for drugs—coupled with the fact that one out of four of the 22 million persons under the poverty line of $1,900 a year is over the age of 65—makes the problem of costly and ineffective drugs an extremely important matter for senior citizens. In view of the importance of drugs and medical care generally to the elderly, the National Council of Senior Citizens was a principal supporter of Medicare, has actively participated in drafting legislation to extend Medicare coverage to out-of-hospital drugs, has worked for consumer representation on the Joint Commission on the Accreditation of Hospitals, and joined with two other organizations in 1966 to form a drug cooperative in an effort to reduce the rising cost of drugs.

The American Public Health Association is a national professional organization whose membership of over 26,000 consists primarily of profesional public health workers, including doctors, nurses, and hospital administrators. The Association, which is 100 years old this year, was organized to provide public-health professionals with a vehicle for influencing national and local public

health policy. It publishes a monthly magazine, the *American Journal of Public Health*, consisting of papers from its membership, and a monthly newspaper, the *Nation's Health*. Concern with this country's drug problem, including drug ineffectiveness, dominated a major part of the 1972 annual meeting of the Association. As a result, several resolutions supporting broader regulation of the drug industry and increased appropriations to the Food and Drug Administration and other federal agencies charged with the responsibility of safeguarding the public's health were adopted by its members.

The filing of a brief as *amici curiae* is timely. The order of the district court in *American Publc Health Ass'n* v. *Veneman* was not issued until October 11, 1972. The plaintiffs in that case did not learn of the decision of the court of appeals in the instant case until the hearing on the order before the district judge. During that hearing, the Food and Drug Administration told the court that the decision of the court of appeals in this case would seriously interfere with, and might even completely prevent, compliance with any order in *American Public Health Ass'n* v. *Veneman* requiring the FDA to proceed expeditiously, within specified time periods, to enforce the 1962 amendments to the Food, Drug and Cosmetic Act. The American Public Health Association and National Council of Senior Citizens have subsequently moved promptly to file a brief *amici curiae* in this case.

The petition of the United States was filed on September 7, 1972, and the response of respondent was filed on October 6, 1972. However, the respondent in this case has filed its own petition for a writ of certiorari based on the same decision of the court of appeals and the response of the government is due on October 31, 1972. Since this motion and the accompanying brief are also being filed on October 31, the parties will not be prejudiced and the case will not be delayed by the granting of this motion.

CONCLUSION

For the foregoing reasons, we respectfully submit that the Motion to File Brief Amici Curiae in Support of the Petition of the United States for a Writ of Certiorari should be granted.

BRUCE J. TERRIS
JOSEPH ONEK

Attorneys for the American Public Health Association and National Council of Senior Citizens

IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-394

ELLIOT RICHARDSON, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners,

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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BRIEF AS AMICI CURIAE IN SUPPORT OF PETITION OF THE UNITED STATES FOR A WRIT OF CERTIORARI ON BEHALF OF THE AMERICAN PUBLIC HEALTH ASSOCIATION AND THE NATIONAL COUNCIL OF SENIOR CITIZENS

STATEMENT OF INTEREST OF AMICI CURIAE

The interest of the American Public Health Association and National Council of Senior Citizens is fully described in the Motion for Leave to File Brief Amici Curiae above.

REASONS FOR GRANTING THE WRIT

Congress passed in 1962 the Harris-Kefauver Amendments to the Food, Drug and Cosmetic Act, 76 Stat. 781, requiring for the first time that drugs sold to the public be shown to be effective for their intended uses. Congress deferred enforcement of the amendments for two years for drugs on the market before 1962. 76 Stat. 788-789. Thus, the Act allowed the marketing of pre-1962 drugs after 1964 only if they had been shown to be effective.

In fact, the 1962 amendments are still substantially unenforced even today. The Food and Drug Administration has found that 628 drugs are "possibly effective" but it has completed action on only 117 of these drugs. Since 102 of these drugs were finally found to be ineffective and only 15 to be effective, it is almost certain that most of the remaining 511 possibly effective drugs are lacking substantial evidence of effectiveness.[2] Similarly, the FDA has found that 197 drugs are "probably effective" and has finished administrative action on only 22. Since 14 of these drugs were found to be ineffective and only 8 to be effective, it is likely that a majority of the remaining 175 drugs will be found ineffective. While the Food and Drug Administration has not supplied *amici curiae* with exact statistics, there are hundreds of additional drugs still on the market which the FDA has found to be ineffective as to all their claimed uses or has found that they are effective for some claimed uses but have not been shown to be effective for other uses.

[2] The Food and Drug Administration has used the labels "ineffective," "possibly effective," "probably effective," and "effective" in its initial evaluations of drugs. In terms of the statute, however, there are only two categories of drugs—drugs which have been shown to be effective on the basis of substantial evidence and drugs which have not. 21 U.S.C. 355(e). Thus, drugs found to be possibly effective or probably effective, like those found to be ineffective, cannot be legally marketed under the statute.

Thus, 10 years after passage of the 1962 amendments and 8 years after Congress intended them to become effective, hundreds of ineffective drugs continue to be sold to the public.

The District Court for the District of Columbia considered this extremely important federal statute in *American Public Health Ass'n* v. *Veneman*, C.A. No. 1847-70. On August 23, 1972, the district court held that the Food and Drug Administration engaged in "intolerable procrastination" in evaluating reports made to it by the National Academy of Sciences concerning the efficacy of drugs and that hearings had been subject to "interminable delay"; that the FDA had extended the two-year grace period for enforcement of the Act "far beyond that envisioned by the statute"; and that it had "effectively stay[ed] implementation of the Congressional mandate that drugs in the marketplace be both safe and effective."

Subsequent to its opinion, the district court issued an order on October 11, 1972, establishing a time schedule for the FDA to complete enforcement of the 1962 amendments concerning pre-1962 drugs. The court ordered that its administrative review be completed within a total of four years—drugs found ineffective by the FDA within one year of the order; possibly effective drugs within the following 18 months; probably effective drugs within the following year; and drugs which were effective as to some uses and less than effective for other uses within the next 6 months. Judge Bryant retained jurisdiction and ordered that the FDA submit reports every six months describing its progress in enforcing the statute.

The decision of the Court of Appeals for the Fourth Circuit in this case greatly expands the right of drug manufacturers to obtain administrative hearings. Section 505(e) of the Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e), requires drug manufacturers to demonstrate the effectiveness of drugs they market by "substantial evi-

dence." Substantial evidence is defined by Section 505 (d) of the Act, 21 U.S.C. 355(d), as "adequate and well-controlled investigations." The FDA has therefore issued regulations providing that drug manufacturers are entitled to hearings only if they produce "adequate and well-controlled clinical investigations to support the claims of effectiveness." 21 C.F.R. 130.14, as amended, 35 Fed. Reg. 7252. The court of appeals below ordered the FDA to grant respondent a hearing although the FDA had found that respondent had submitted no evidence meeting the statutory definition of "substantial evidence" and therefore no issue was properly raised for the hearing.

The hearing afforded by the court of appeals does not protect any legitimate rights of drug manufacturers. The Food, Drug and Cosmetic Act and implementing regulations define the kinds of evidence which the FDA may consider. Manufacturers have had 10 years to conduct tests meeting the statutory requirements. A drug manufacturer is of course entitled to a hearing where it presents some "substantial evidence" as defined by the statute. No purpose, however, is served by granting a hearing where the manufacturer's only evidence must, and will inevitably, be rejected by the FDA. The only effect of the decision below will therefore be to afford opportunities to drug manufacturers for further delay in removing ineffective drugs from the market.

The decision of the court of appeals may have serious effects for carrying out the district court's order in *American Public Health Ass'n* v. *Veneman* and for enforcement of the 1962 amendments. During the hearings before Judge Bryant concerning the order, the Food and Drug Administration repeatedly represented that it would be unable to comply with the deadlines in the order and would require years of additional time if it were required to afford hearings to drug manufacturers whenever evidence was submitted of effectiveness even though this

evidence did not consist of "adequate and well-controlled investigations" as required by the Act. If hearings can be obtained on the basis of such evidence, it is likely that most manufacturers will request them since they are entitled to continue selling drugs until the hearing is held and a subsequent determination is made. The FDA noted that a recent drug hearing had taken 3 months to complete. *In the Matter of SERC Tablets*, Unimed, Inc., Docket No. FDCD-111, 1969. The FDA contended that it does not have the hearing examiners, attorneys, scientists, or other resources to handle hundreds of lengthy administrative hearings expeditiously.[3]

Amici curiae do not accept the suggestion that the FDA need not comply with the district court's order if the decision of the court of appeals is not reversed. We believe that the FDA and the Executive Branch still have the duty to enforce the 1962 amendments to the Food, Drug and Cosmetic Act. If the FDA does not have the personnel to afford legally necessary procedures and still enforce the law, the FDA and the rest of the Executive Branch are legally required to seek additional funds.

Nevertheless, *amici curiae* strongly support the position of the Food and Drug Administration in this case. The decision of the Court of Appeals for the Fourth Circuit will allow manufacturers to delay even further the withdrawal of ineffective drugs from the market. It will seriously interfere with prompt enforcement of the 1962 amendments which should long ago have required the withdrawal of all ineffective drugs from the

[3] The FDA has similarly stated in its petition for a writ of certiorari in this case (p. 17, note 9) that "[m]anifestly, the agency will be unable to satisfy the thrust of that decision [in *American Public Health Ass'n* v. *Veneman*] to expedite review and appropriate withdrawal actions if it must meet the standard for granting evidentiary hearings prior to withdrawal that has been imposed by the court of appeals in the instant case."

market. It will consume manpower urgently needed by the FDA to enforce not only the 1962 amendments, but other provisions of the Food, Drug and Cosmetic Act and other statutes. We therefore submit that this case raises issues of substantial national importance involving the ability of the Food and Drug Administration to enforce important federal statutes designed to protect the public health.

CONCLUSION

For the foregoing reasons, we respectfully submit that the petition of the United States for a writ of certiorari should be granted.

BRUCE J. TERRIS
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APPENDIX A

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

Civil Action No. 1847-70

[Filed Aug. 23, 1972—James F. Davey, Clerk]

AMERICAN PUBLIC HEALTH ASSOCIATION AND NATIONAL COUNCIL OF SENIOR CITIZENS,
Plaintiffs,

v.

JOHN G. VENEMAN, Acting Secretary of the Department of Health, Education and Welfare, and CHARLES EDWARDS, Commissioner of the Food and Drug Administration,
Defendants.

MEMORANDUM AND ORDER

I

Before the court are the cross-motions of the parties for summary judgment. Because of the complex nature of this case, a detailed recitation of the facts is appropriate.

In 1962, the Congress amended the Food, Drug, and Cosmetic Act of 1938 to require that all drugs on the market be proven effective for their suggested use.[1] Under 21 U.S.C. § 355(e) (1970),

> The Secretary shall, after due notice and opportunity for a hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds . . .

[1] P.L. 87-781. The pertinent amendments are codified in 21 U.S.C. §§ 355, 357 (1970 ed.).

> (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof. . . .

Section 355 relates solely to non-antibiotic drugs. Under § 357(h), antibiotic drugs may be ordered withdrawn when

> (2) the Secretary finds, on the basis of new information with respect to such drug evaluated with the information before him when the application under section 355 of this title became effective or was approved, that there is a lack of substantial evidence (as defined in section 355(d) of this title) that the drug has the effect it purports or is represented to have under such conditions of use.

The term "substantial evidence," as used in §§ 355(e) and 357(h) means

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. 21 U.S.C. § 355(d) (1970).

Under the terms of P.L. 87-781, Section 107(c)(3)(B), the effectiveness requirement did not take effect until October 10, 1964, two years after enactment of the statute. The Food and Drug Administration in 1964

promulgated regulations to require the drug manufacturers to report whether approved drugs were still being marketed in conformity with the conditions for which they had been approved and to submit scientific data in support of any claims in promotional material which departed from the approved labeling. The drug industry failed to comply, and litigation instituted in the District of Delaware by the Pharmaceutical Manufacturers Association challenging the legality of the regulation was still pending as of September 3, 1970.[2]

In 1966, Dr. James Goddard became Commissioner of FDA and began to move ahead with efficacy studies of the various drugs. In July of 1966, a contract with the National Academy of Sciences-National Research Council was signed, whereby the NAS-NRC was to review the efficacy of all drugs which had been given FDA approval from 1938 to 1962. The FDA then published orders in the Federal Register requiring the drug manufacturers to submit certain information regarding each approved drug, including references to evaluations of the effectiveness of the drug. The purpose was to permit the manufacturers the "opportunity to identify the best available evidence which they believed supported the claims made for the drug."[3] After several extensions, the manufacturers were required to submit their information by July 1, 1967.[4] NAS-NRC began submitting its first reports on October 11, 1967, and submitted the last report on April 15, 1969; there were 2,824 reports submitted, covering approximately 3,700 drugs manufactured by 237 companies.

In January, 1968, the FDA began implementation of the NAS-NRC reports. The procedure adopted has

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[2] Affidavit of Charles C. Edwards, filed September 4, 1970, p. 3.

[3] Affidavit of Charles C. Edwards, *supra*, Note 2, pp. 5-6.

[4] It should be noted that this date is nearly three years after the effective date of §§ 355 and 357.

been to evaluate each report and to release it to the public only after the FDA evaluation is completed. When the FDA completes its evaluation of an NAS-NRC report, an announcement is made in the Federal Register that the FDA has concluded that the drugs involved are "effective," "probably effective," "possibly effective," or "lack substantial evidence of effectiveness"; the first three classifications are the same as those used in the NAS-NRC reports, but the last seems to be an FDA substitution for the NAS-NRC classification "ineffective."

After announcing the classification of a drug in the Federal Register, the FDA affords the drug manufacturer a period of time to provide additional data to the FDA in every case where the drug is classified as anything other than "effective." The manufacturer is given 12 months or 6 months where the drug is listed as probably or possible effective, respectively,[5] and 30 days where the drug is classified as lacking substantial evidence of effectiveness.[6] During this time period, the manufacturer is permitted to continue marketing the drug. If, at the end of the interim period, no studies have been undertaken by the manufacturer, or if the studies do not provide substantial evidence of effectiveness, procedures are supposed to be instituted to withdraw approval of the drug pursuant to 21 U.S.C. § 355(e).[7]

When the Secretary finds that a drug lacks substantial evidence of efficacy, §§ 355(e) and 357(h) & (f) require that there be an opportunity for a hearing. 21 C.F.R. § 130.27 (1971) prescribes the procedure for withdrawal of non-antibiotic drugs. The Secretary is required

[5] See Conditions for Marketing New Drugs Evaluated in Drug Efficacy Study, 35 Fed. Reg. 11273 (1970).

[6] See, e.g., 35 Fed. Reg. 12423 (1970).

[7] See Conditions for Marketing New Drugs, *supra*, Note 5. It is unclear from the record whether this procedure has been applied to antibotics.

to notify the holder of a new drug application of an opportunity for a hearing on the proposed withdrawal, and notice must be published in the Federal Register. The manufacturer has 30 days then to avail himself of the hearing opportunity.[8] If the manufacturer fails to avail himself of the opportunity for the hearing, the FDA may enter a final order withdrawing the drug.[9] When a manufacturer desires to have a hearing, he must respond within the 30 days after notice is published, giving reasons, supported by an analysis of clinical and investigative data which he would present at the hearing in support of his opposition to withdrawal of the drug.[10] The FDA may refuse a hearing and withdraw the drug where the data presented is insufficient on its face to support a claim of effectiveness.

Though the language of 21 C.F.R. § 130.14(b) (1971) is ambiguous, it appears that a hearing, when permitted, must commence as soon as practicable. After the hearing the examiner submits tentative findings of facts and an order which becomes final if no objection is made within 20 days thereafter. The Commissioner of the FDA then issues the final order. The procedure followed in the cases of antibiotic drugs is contained in 21 C.F.R. § 146.1 (1971) and is sufficiently similar as to not require separate discussion.

II

As a preliminary matter, the question of jurisdiction is quickly resolved. The defendants contend that the matters in controversy are within the agency's discretion and are thus subject neither to mandamus nor judicial review. The court has considered both the allegations of the complaint and the merits and concludes, as will

[8] 21 C.F.R. § 130.14(a) (1971).

[9] 21 C.F.R. § 130.15 (1971).

[10] 21 C.F.R. § 130.14 (1971).

be shown later in this memorandum, that the issues presented do not deal with agency discretion and are subject to review under the Administrative Procedure Act.[11]

III

The plaintiffs' complaint challenges in several respects the manner in which the FDA is administering Sections 355 and 357.

A.

First the plaintiffs assert that the FDA practice of granting manufacturers time to bolster the record regarding a drug's effectiveness, after the FDA has publicly concluded that a drug is less than effective, is a violation of the statutory mandate. The statute states unequivocably that

> The Secretary *shall* . . . withdraw approval of any application with respect to any drug under this section if the Secretary finds . . . that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed . . . 21 U.S.C. § 355 (e) [Emphasis added].

While § 355(e) pertains only to non-antibiotic drugs, 21 C.F.R. § 146.1(g)(1) (1971) declares that

> No regulation providing for the certification of any batch [of antibiotic drugs] . . . and no existing regulation will be continued in effect unless it is established by substantial evidence that the drug will have such characteristics . . . to adequately insure safety and efficacy of use.

Thus it could not be clearer that the Secretary *must* begin the procedures to withdraw a drug when he concludes that there is no substantial evidence of efficacy. The defendants contend that the many announcements

[11] 5 U.S.C. §§ 701-706 (1970).

which have been published in the Federal Register regarding FDA conclusions about the efficacy of various drugs are not findings by the agency [12] and that the FDA is "not required by law to notice the cases [where a drug has been found less than effective] or press them to hearing immediately upon its announcement of the NAS-NRC findings and its concurrence. It has discretion in the selection of cases to notice for hearing." [13] This argument is unpersuasive in view of the clear language of the statute and regulations and the Congressional intent to rid the marketplace of ineffective drugs.[14]

B.

The plaintiffs' second claim is that once the FDA commences the procedure outlined in the statute or regulation for withdrawing a drug, it fails to adhere to those procedures. Plaintiffs assert, and the defendants do not refute it, that for many drugs the FDA has published in the Federal Register the required notice of an opportunity for a hearing and that the manufacturers have failed to avail themselves of the opportunity for

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[12] Defendants' Reply Brief, p. 2.

[13] Defendants' Memorandum in Support of Defendants' Motion to Dismiss and for Summary Judgment, p. 20.

[14] The court feels compelled to state that even if the statute and regulation did not require immediate action by the FDA to withdraw an ineffective drug, the court would grant mandamus based upon not only the statute, but also the failure of the FDA to adhere to its regulation declaring that a drug would be withdrawn at the end of a 30 day, 60 month or 12 month period. 35 Fed. Reg. 11273 (1970). See pp. 30-32 of Plaintiffs' Memorandum in Support of Motion for Summary Judgment. Furthermore, the court cannot understand the solicitude of the FDA for the drug manufacturers in giving additional time to supplement the record when in all cases the manufacturers have been on notice regarding the statute's efficacy requirement for at least four or more years. The hearing procedure provides ample opportunity for drug manufacturers to produce their scientific evidence, when they have any, in opposition to withdrawal.

the hearing within the required 30 days; nevertheless the FDA has failed to withdraw these drugs from the market. In these circumstances, the withdrawal is both required by the statute and purely a ministerial duty, and failure to withdraw constitutes agency action unlawfully withheld.

In addition, plaintiffs contend that where drug manufacturers have requested a hearing, such hearings have been a long time in coming. They cite as examples two drugs where no hearing had been scheduled at the time the plaintiffs filed their memorandum, even though the manufacturers had requested hearings one and a half years before. Indeed, this situation was commented upon unfavorably in *U. S. V. Pharmaceutical Corporation* v. *Secretary, HEW*, No. 24,900, slip op. at 14 (D.C. Cir. August 14, 1972). As the court reads 21 C.F.R. § 130.14(b), a hearing on withdrawal of a new drug application is to be scheduled as soon as practicable, and while such a provision confers some agency discretion in scheduling the hearing, interminable delay obviously is not contemplated.

C.

Plaintiffs also claim that the FDA has failed to exercise its authority to immediately suspend drugs which present an imminent hazard to the public health.[15] The invocation of this emergency procedure is a matter which is peculiarly one of judgment, and while the agency has been, perhaps, overcautious on occasion in view of the lengthy delays in removing drugs from the market, the record before the court is inadequate to support a finding of an abuse of discretion.

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[15] 21 U.S.C. § 355(e) (1970) and 21 C.F.R. § 146.1 (1971).

IV

When the final motion paper was filed in this case on December 1, 1970, less than half of the NAS-NRC report had been evaluated and published.[16] In his affidavit filed September 4, 1970, the defendant Commissioner of the FDA stated

> In summary, it is expected that all the reports will be released and FDA and Academy findings published prior to July 1, 1971.[17]

In response to the court's inquiry the defendants advised the court on February 2, 1972, that 814 reports still had not been evaluated by the FDA. Of these outstanding reports, 327 had been returned to NAS-NRC for further evaluation in early 1971 and were reported on by NAS-NRC in October, 1971; they are presently being reevaluated by the FDA. In addition, the FDA has advised that the 260 NAS-NRC reports on over-the-counter drugs will not be rated by the FDA (and hence will remain unpublished) because it has announced a new program with regard to over-the-counter drugs.[18] The plaintiffs have protested that the proposed procedures are "enormously elaborate" and will create extensive delay in applying the efficacy requirement to over-the-counter drugs. The court shares this concern, since over-the-counter drugs are purchased without medical advice in most cases, and an NAS-NRC report on over-the-counter drugs indicates that only 25% of all such drugs are effective.[19]

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[16] Defendants' Reply Brief, p. 6, indicates that 1188 out of 2771 NAS-NRC reports have been published.

[17] Affidavit of Charles C. Edwards, *supra*, Note 2, p. 12.

[18] 37 Fed. Reg. 85 (1972).

[19] Id. at 85. The type of intolerable procrastination in the FDA evaulation of NAS-NRC reports has been dramatically evidenced very recently. The FDA has just released for publication an NAS-

Because the FDA has responsibility in matters which directly and literally affect the nation's health and welfare, it is one of the most important of all Federal regulatory agencies. Its enforcement stance must be well balanced, but nevertheless effective. A timid approach can vitiate whatever protection the Congress has created for the consumer. On the other hand, an overly zealous approach can ruin a drug manufacturer by destroying public confidence in its products. Thus, it is understandable that the agency might have legitimate concern for drug manufacturers who must comply with new statutory requirements, and surely the question of time necessary to adduce new evidence of efficacy is an important consideration in creating an administrative scheme for implementation of the statute.

However, the FDA must remember that it does not stand alone in this regard. At the very outset the Congress also was sensitive to this problem, and allowed a two-year grace period before the 1962 amendments were to become effective. When, as is the case here, the Congress has shown an awareness of a problem and has acted accordingly, it seems inappropriate for an agency to adopt procedures which extend the grace period far beyond that envisioned by the statute, and which effectively stay implementation of the Congressional mandate that drugs in the marketplace be both safe and effective.[20]

NRC report on over-the-counter drugs, specifically cold remedies, that was submitted to the FDA three years ago. The report indicates that many of the nation's leading cold medications lack substantial evidence of effectiveness and are subject to withdrawal. Washington Post, July 8, 1972, p. 2.

[20] The defendants cite *Pfizer, Inc.* v. *Richardson*, 434 F.2d 536 (CA2 1970) and *Pharmaceutical Manufacturers Assn.* v. *Richardson*, 318 F.Supp. 301 (D.Del. 1970) as "specifically approv[ing] the procedures adopted by the defendants for the implementation of the NAS-NRC Drug Efficacy Study," but their reliance on these cases is

Based upon the entire record in this case, the court concludes that there is no compelling reason why the remaining NAS-NRC reports should not be immediately released, that it would be an abuse of agency discretion to refuse to make such reports public, and that the court should set a deadline for the FDA to complete its evaluation of all drugs with regard to efficacy.

Accordingly, the plaintiffs' motion for summary judgment is granted, and the defendants' motion to dismiss and for summary judgment is denied.

Counsel are directed to present an appropriate order.

/s/ William B. Bryant
Judge

Dated: August 23, 1972

misplaced, since they deal with the validity of FDA regulations regarding the definition of "substantial evidence" and the right to a hearing prior to withdrawal of a drug. Neither case deals with the issues before this court.

APPENDIX B

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

Civil Action No. 1847-70

[Filed Oct. 11, 1972—James F. Davey, Clerk]

AMERICAN PUBLIC HEALTH ASSOCIATION, et al.,
Plaintiffs,

v.

JOHN G. VENEMAN, et al.,
Defendants.

ORDER

Pursuant to this Court's Memorandum and Order entered August 23, 1972, it is hereby ordered that:

I. Defendants shall release and make available to the public immediately all reports of the National Academy of Sciences-National Research Council (NAS-NRC) relating to the effectiveness of drugs approved for marketing between 1938 and 1962, which have previously been received by the Food and Drug Administration and not heretofore released, and shall release all such reports received in the future immediately upon receipt.

II. Defendants shall proceed expeditiously, using available resources and personnel to the maximum extent feasible consistent with its other obligations under the law, to complete implementation of the drug effectiveness review with respect to human drugs as soon as possible.

III. Within 120 days from the date of this Order, defendants shall evaluate all NAS-NRC reports for drugs not previously evaluated, and publish in the Federal Register an evaluation of each product as "effective," or "less than effective." For purposes of setting implementation priorities, each "less than effective" drug shall

be further classified as "probably effective," "possibly effective," or "ineffective" for each of its multiple indications. For a drug with multiple indications, overall classification of the drug shall depend on the highest evaluation given to any one of its multiple indications. Defendants may defer such evaluation for a limited number of drugs where further clarification from the NAS-NRC is requested or where further consultation with outside experts is pursued; in these situations a report shall be filed with the court which shall be available for public inspection, and evaluation shall proceed as rapidly as is feasible.

IV. Defendants shall, beginning immediately, proceed to implementation of the drug effectiveness review with respect to human prescription drugs classified as "ineffective," in accordance with the following procedures, priorities, and time limitations:

A. For each drug subject to paragraph III which is classified as "ineffective," a Notice of Opportunity for Hearing on a proposal to withdraw approval of the new drug application or form 5 for such drug shall be published in the Federal Register concurrently with the publication on that evaluation.

B. Within 60 days from the date of this Order, a Notice of Opportunity for Hearing shall be published for all drugs previously classified in an evaluation published in the Federal Register as "ineffective" but for which such a Notice has not yet been published, unless a review of new data or information results in reclassification of the drug. If the drug is reclassified, an appropriate notice shall be published in the Federal Register and implementation with respect to the drug shall be handled as set out below.

C. With respect to each drug previously classified as "ineffective" and for which a Notice of Opportunity for Hearing has already been published in the Federal Register, a final order shall be published in the Federal Register ruling on such Notice as follows:

(1) within 60 days from the date of this Order, where no request for hearing has been filed in response to the Notice of Opportunity for Hearing within the statutory time limit or where a request for hearing is supported by no data or information whatever; and

(2) within 150 days from the date of this Order, where a request for hearing supported by data and information has been filed in response to such proposal.

D. Within 12 months of this Order, for a drug determined to be "ineffective" and for which a Notice of Opportunity for Hearing has been published pursuant to paragraphs IV(A) and (B) of this Order, a final order shall be published in the Federal Register ruling upon such request for hearing.

E. Work on administrative hearings and on court actions with respect to withdrawal of new drug applications and form 5's for drugs classified as "ineffective" and removal of other marketed drugs covered by such applications and form 5's shall take precedence over work on drugs classified as "possibly" or "probably effective" or as "effective."

V. Defendants shall proceed to implementation of the drug effectiveness review with respect to human prescription drugs classified as "possibly effective," in accordance with the following procedures, priorities, and time limitations:

A. Within 15 months of this Order a Notice of Opportunity for Hearing shall be published in the Federal Register.

B. Within 30 months of this Order a final order ruling on any request for hearing filed within the statutory time limit in response to a Notice under subparagraph A above shall be published in the Federal Register.

C. Work on administrative hearings and on court actions with respect to withdrawal of new drug applications and form 5's for drugs classified as "possibly effective" and removal of other marketed drugs covered by such applications and form 5's shall take precedence over work on drugs classified as "probably effective" or as "effective."

VI. Defendants shall proceed to implementation of the drug effectiveness review with respect to human prescription drugs classified as "probably effective" in accordance with the following procedures, priorities, and time limitations:

A. Within 33 months of this Order a Notice of Opportunity for Hearing shall be published in the Federal Register.

B. Within 42 months of this Order a final order ruling on any request for hearing filed within the statutory time limit in response to a Notice under subparagraph A above shall be published in the Federal Register.

C. Work on administrative hearings and on court actions with respect to withdrawal of new drug applications and form 5's for drugs classified as "probably effective" and removal of other marketed drugs covered by such applications and form 5's shall take precedence over work on drugs classified as "effective."

VII. Defendants shall proceed to implementation of the drug effectiveness review with respect to human prescription drugs classified as "effective" but with one or more less than effective indications pursuant to 21 U.S.C. 355(e) in accordance with the following procedures, priorities, and time limitations:

A. Within 45 months of this Order and after a refusal to delete all less than effective indications a Notice of Opportunity for Hearing shall be published in the Federal Register.

B. Within 48 months of this Order a final order ruling on the request for hearing filed within the statutory time limit in response to a Notice under subparagraph A above shall be published in the Federal Register.

VIII. Defendants may implement the drug effectiveness review with respect to any specific "possibly effective" or "probably effective" or "ineffective" drug not in accordance with the priorities established in paragraphs IV-VII where public health considerations or administrative efficiency justify such action.

IX. An order to withdraw the drugs shall be issued concurrently with any denial of a request for a hearing made under paragraphs IV(C), IV(D), V(B) of this Order. Defendants may grant a stay of such order in appropriate cases.

X. Defendants shall not grant any extension of time for any request for a hearing or other response to a Notice of Opportunity for Hearing.

XI. Any Notice of Opportunity for Hearing shall permit any person with an interest in an identical, related or similar product which is covered by the new drug application or antibiotic monograph an opportunity to submit data and information on the effectiveness of

the drug and a statement why the new drug application or form 5 should not be withdrawn and/or why a hearing should be held to consider the matter.

XII. Defendants shall schedule and conduct administrative hearings, when required by 21 C.F.R. 130.14(B), as expeditiously as practicable.

XIII. Upon withdrawal of a new drug application of form 5, Defendants shall make a good faith effort to find all identical, related, or similar products which are covered by the new drug application or antibiotic monograph and shall proceed to remove them from marketing as expeditiously as possible.

XVI. A limited number of drugs may remain on the market pending completion of scientific studies to determine effectiveness where there is a compelling justification of the medical need for the drug. Such justification shall be made by Defendants in writing, shall be filed with the Court, and shall be available for public inspection.

XV. Over-the-counter human drugs which are the subject of NAS-NRC reports shall be reviewed and handled pursuant to the procedure established in the Federal Register of May 11, 1972 (37 F.R. 9464 et seq.).

XVI. This Order does not affect the interim labeling and advertising requirement imposed by the Food and Drug Administration in the Federal Register of June 8, 1971 (36 F.R. 11022) and February 12, 1972 (37 F.R. 3175).

XVII. Six months after the date of this Order, and every six months thereafter until completion of the implementation of the drug effectiveness review, a report on the actions implementing this Order shall be submitted to this Court and shall be available for public inspection.

Such reports shall include:

(1) Statistical data showing actions taken on
of the various categories of drugs during the prev
six months and the number of drugs in the va
stages of review;

(2) Statistical data on work yet to be accompli
in the drug effectiveness review according to the va
categories of drugs and the various stages of revie

(3) The number and kinds of personnel who
assigned to the drug effectiveness review at the
and the conclusion of the previous six months and
estimated time each category of personnel spent on
review during this period;

(4) The predicted number and kinds of perso
who will be assigned to the drug effectiveness re
during the next six months and the estimated time
category of personnel will spend on the review dur
this period;

(5) Detailed information concerning any failure
comply with this Order and the reasons for this fail
and

(6) Any problems anticipated for the next six mo
in complying with this Order and possible methods
overcoming these problems.

XVIII. The Court expressly retains jurisdiction o
this proceeding to amend or modify any provisions
this Order as may be required.

/s/ William B. Bryant
Judge

October 10, 1972
Date

IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-666

USV PHARMACEUTICAL CORPORATION, PETITIONER

v.

ELLIOTT L. RICHARDSON, SECRETARY OF HEALTH, EDUCATION AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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REPLY MEMORANDUM FOR PETITIONER

Because the government has agreed that the petition for certiorari should be granted (Resp. Mem., p. 6) we need not now consider the arguments pressed in defense of the judgment below. The timetable suggested by the government in the event certiorari is granted in this and the related cases, however, requires comment.

USV concurs in the desirability of "grouping", in some logical fashion, the issues presented by these cases. But we fear that the grouping proposed by the government would result in a disorganized and unstructured over-all presentation, if adopted for oral argument.

Contrary to the government's suggestion (Resp. Mem., p. 13), the issues of statutory construction relating to the grandfather clause in the 1962 Drug Amendments (the questions presented in this case and Question 4 in the *Hynson* cross-petition [1]) are entirely distinct from *Hynson's* Question 2. That question relates to whether an evidentiary hearing would be required in administrative proceedings to decide if a product is a "new drug", assuming that the agency rather than the court is the proper forum. *Hynson's* Question 2 should appropriately, therefore, be grouped with the government's petition in *Hynson*,[2] which puts in issue the circumstances in which an evidentiary hearing is required in administrative proceedings to decide the actual safety and effectiveness of drugs. Consolidated oral argument on *Hynson's* issue of proper adjudicatory procedure and on the questions presented in *USV* as to the substantive criteria for grandfather protection would confuse, rather than clarify, this complex and important litigation.

There is also need to modify the government's further proposal to curtail oral argument on the substantive questions of interpreting the grandfather clause. In total, at least three separate such issues are

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[1] *Hynson, Westcott & Dunning, Inc.* v. *Richardson*, No. 72-414, *petition for certiorari filed*, Sept. 11, 1972.

[2] *Richardson* v. *Hynson, Westcott & Dunning, Inc.*, No. 72-394, *petition for certiorari filed*, Sept. 7, 1972.

tendered by the two petitions in this group (the present case and the *Hynson* cross-petition, No. 72-414). Only one of these issues is even partly common to both petitions (Question 1 in *USV* and Question 4 in the *Hynson* cross-petition), and even with respect to that common element the rationales of the respective petitioners are different.[3]

We suggest, therefore, that oral argument would be most helpful to the Court if the usual one hour were allowed in the present case. The effect would merely be to increase the total time allowed for oral argument in these cases from the three and one-half hours proposed by the government to four hours.

Finally, we suggest that, if the petitions for certiorari are granted, the "jurisdictional" issues presented by *Bentex* (No. 72-555) and *Ciba* (No. 72-528), relating to the respective roles of court and agency, should be argued first. We propose that the "jurisdictional" argument be followed immediately by oral argument on the issues of statutory construction arising under the grandfather clause presented here and in *Hynson* (No. 72-414), leaving for last the issues of hearing procedure presented by the two petitions in *Hynson*.

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[3] Hynson appears to argue that when a drug became no longer "new" prior to 1962 it was *ipso facto* no longer "covered by an effective [new drug] application", while our approach concedes arguendo that "there must be some further action which removes the product from new-drug regulation, before it can be found the product is no longer 'covered' by an effective NDA" (Pet., p. 18). Moreover, only the *USV* petition (Question 2) presents the issue of the status of up to 13,000 "me-too" products. Conversely, we do not raise *Hynson's* Question 3 as to the authority of FDA to conduct proceedings to withdraw approval of pre-1962 NDA's for products protected by the grandfather clause.

This sequence of argument, because it tracks logical sequence of issues as they normally would reached in a given case, would promote clarity in p sentation and assist the Court in examining the en regulatory framework in which these related c arise.

Counsel for Bentex Pharmaceuticals, Inc. *et al.* (spondents in No. 72-555) and for Ciba Corp. (p tioner in No. 72-528) have authorized us to state t they join in the foregoing suggestion for the sequen of oral argument in these cases if the petitions f certiorari are granted.

Respectfully submitted,

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January 3, 1973

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In the Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-394

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, PETITIONERS

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

BRIEF FOR THE PETITIONERS

OPINIONS BELOW

The opinion of the court of appeals (J.A. 173-180)[1] is reported at 461 F. 2d 215. The order of the Commissioner of Food and Drugs was published in the Federal Register on June 18, 1971 (J.A. 72-78; 36 Fed. Reg. 11763).

[1] "J.A." refers to the Joint Appendix filed by the parties in this case and in Nos. 72-414, 72-528, 72-555, and 72-666, with which this case has been consolidated.

JURISDICTION

The judgment of the court of appeals (J.A. 181) was entered on May 24, 1972. The petition for a writ of certiorari was filed, pursuant to an extension of time granted by Mr. Justice Rehnquist, on September 7, 1972. On January 8, 1973, this Court granted the petition and consolidated the case with four other cases in which it also granted writs of certiorari.[2] The jurisdiction of this Court rests on 28 U.S.C. 1254(1) and 21 U.S.C. 355(h).

QUESTION PRESENTED

Whether the Commissioner of Food and Drugs may, in implementing the drug effectiveness requirements of the 1962 amendments to the Food, Drug, and Cosmetic Act of 1938, withdraw approval for the marketing of a drug for lack of proof of effectiveness, without a hearing, if the manufacturer has failed to comply with the Commissioner's regulations requiring that a request for hearing must be supported by a showing that it is prepared to produce the kind of "substantial evidence" of effectiveness required by the statute.

STATUTORY PROVISIONS AND REGULATIONS INVOLVED

Section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)) (J.A. 479) provides in pertinent part:

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[2] The other cases are *Hynson, Westcott and Dunning, Incorporated* v. *Caspar W. Weinberger, et al.*, No. 72-414; *CIBA Corporation* v. *Caspar W. Weinberger, et al.*, No. 72-528; *Caspar W. Weinberger, et al.* v. *Bentex Pharmaceuticals, Inc., et al.*, No. 72-555; and *USV Pharmaceutical Corporation* v. *Caspar W. Weinberger, et al.*, No. 72-666.

> The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds * * * (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect its purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof * * *.

Section 505(d) (21 U.S.C. 355(d)) (J.A. 478) provides in pertinent part:

> * * * As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

Pertinent provisions of the regulations of the Commissioner of Food and Drugs, 21 C.F.R. 130.12(a)(5) and 130.14, as amended, 35 Fed. Reg. 7251, 7252, are set forth at J.A. 487–491.

STATEMENT

In 1953, Hynson, Westcott and Dunning, Incorporated ("Hynson") filed a new drug application ("NDA") for its drug Lutrexin (J.A. 3–4) with the Food and Drug Administration ("FDA"), pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)). Hynson recommended the drug, whose active ingredient, lututrin, is an extraction of pig ovaries, for use in the treatment of premature labor, threatened and habitual abortion, and dysmenorrhea (J.A. 3, 73, 166). The FDA, after examining the studies submitted with the application, informed Hynson that the studies were not sufficiently well controlled to justify the claims of effectiveness, and it particularly urged the manufacturer not to represent the drug as useful for threatened and habitual abortion (J.A. 3–4). However, because under the statute in effect at that time FDA was obliged to evaluate new drug applications solely upon consideration of the drug's safety, it permitted the NDA for Lutrexin to become effective in December 1953 (J.A. 3–4).[3] Two years later Hynson filed an NDA for Trexinest, another lututrin drug for which it made the same claims presented earlier for Lutrexin, and FDA, again on the basis of safety, permitted

[3] A review of the general background and history of the 1938 Act and the 1962 amendments thereto and FDA's administration of the legislation is set forth in our brief in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72–555.

the NDA to become effective in 1956 (J.A. 4–5, 8–10).[4]

The 1962 Drug Amendments require FDA[5] to appraise drugs on the basis of their effectiveness for claimed uses as well as their safety. Accordingly, FDA contracted in 1966 with the National Academy of Sciences-National Research Council ("NAS–NRC") to assist it in the enormous task of reviewing efficacy claims for all drugs approved (as safe) between 1938 and 1962.[6] By order issued July 6, 1966, the Commissioner directed the holders of NDAs issued between 1938 and October 10, 1962, to submit the "most pertinent" data available concerning the effectiveness of their drugs (J.A. 193; 31 Fed. Reg. 9426). Hynson submitted a list of literature references, a copy of an unpublished study, and a representative sample testimonial letter on behalf of Lutrexin (J.A. 5–6).

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[4] In addition to 500 units of lututrin, each tablet of Trexinest contained 1.0 milligram of sodium estrone sulfate (J.A. 9). The effectiveness of sodium estrone sulfate is not questioned. Rather, the issue with Trexinest was whether the addition of lututrin brought any therapeutic benefits not conferred by the sodium estrone sulfate. Hynson has now discontinued the marketing of Trexinest.

[5] The Act speaks in terms of the Secretary of Health, Education, and Welfare. However, the Secretary has delegated this authority to the Commissioner of Food and Drugs. See 21 C.F.R. 2.120.

[6] A good description of the work and general conclusions of the NAS–NRC Study is found in *Drug Efficacy Study*, Final Report to the Commissioner of Food and Drugs, Food and Drug Administration, From the Division of Medical Sciences, National Research Council, National Academy of Sciences, Washington, D.C. (1969) (hereafter "NAS–NRC Report"). Ten copies of the study have been lodged with the Clerk of this Court.

496-754—73——2

An NAS–NRC panel on drugs used in disturbances of the reproductive system reported to FDA that Hynson's claims of Lutrexin's effectiveness were either "inappropriate" or "unwarranted" in the absence of submission of further, proper documentation. The panel pointed out that the studies relied upon by the manufacturer were not well controlled, and it concluded that the drug was only "possibly effective" for its intended uses (J.A. 7–8).

On May 24, 1968, the Commissioner, after reviewing the report of the NAS–NRC panel, invited Hynson to submit further and sound documentation on the efficacy of Lutrexin (J.A. 10–11). Hynson submitted additional data (J.A. 28–29), but the Commissioner concluded that this additional information still failed to provide substantial evidence of the effectiveness of lututrin (J.A. 12). Accordingly, on March 22, 1969, he published notice of his intention to withdraw approval of Hynson's NDAs and offered Hynson the opportunity for a prewithdrawal hearing (J.A. 12–14). At that time, the agency's rules provided for a hearing upon timely request by any adversely affected party, and Hynson requested a hearing on April 18, 1969 (J.A. 14).

Before the hearing could take place, however, Hynson, on August 19, 1969, filed suit in the United States District Court for the District of Maryland seeking a declaratory judgment that its drugs were exempt from the efficacy review provisions of the 1962 Drug Amendments, or alternatively that there was no lack of substantial evidence of the drugs' efficacy (J.A.

15). The government responded with a motion to dismiss.

While the district court litigation was pending, FDA, on May 8, 1970, promulgated new regulations establishing minimal standards for "adequate and well-controlled investigations" as required under Sections 505(d) and 505(e) of the Act and limiting the right to a hearing to those applicants who supported their requests by a showing that such evidence exists (J.A. 487-491).[1] Shortly thereafter, the Commissioner wrote to Hynson asking the manufacturer to amend its request for hearing to provide supplementary data that would bring the request into compliance with the new regulations (J.A. 20-21). Hynson declined to amend its request, taking the position that its right to a hearing had already vested under the rules in effect at the time of its original request (J.A. 21-23).

FDA and Hynson agreed that, pending disposition of Hynson's suit by the district court, FDA would take no further steps in the withdrawal proceeding

[1] FDA had originally issued the regulations, in somewhat different form, on September 19, 1969. 34 Fed. Reg. 14596. However, on January 16, 1970, in an unrelated proceeding, the federal district court in Delaware enjoined the agency from carrying out the new regulations, holding that FDA had engaged in rule-making without conforming to the notice requirements of Section 4 of the Administrative Procedure Act. *Pharmaceutical Manufacturers Association* v. *Finch*, 307 F. Supp. 858 (D. Del.). FDA then solicited public comment and reissued the regulations, with certain changes, on May 8, 1970. The court subsequently upheld these regulations against a range of challenges, both substantive and procedural, in *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del.).

(J.A. 22–23). On September 16, 1970, Judge Northrup granted the government's motion to dismiss, ruling that FDA had primary jurisdiction and that Hynson had failed to exhaust its administrative remedies (J.A. 23–24).

After losing its lawsuit, Hynson, on October 16, 1970, renewed its request for an administrative hearing (J.A. 24), asking FDA to determine three questions: (1) whether there was a lack of substantial evidence of Lutrexin's effectiveness; (2) whether the drug was "grandfathered" under Section 107(c)(4) of the 1962 Drug Amendments; and (3) whether the drug was, because of alleged current general recognition of safety and effectiveness, not a new drug (J.A. 26). Although continuing to claim a vested right to a hearing under the former rules, Hynson submitted a list of material previously submitted to NAS-NRC or FDA, which it claimed constituted substantial evidence of Lutrexin's effectiveness under the new rules (J.A. 27–30). It also accompanied its request for a hearing on the jurisdictional questions with certain affidavits and reports of medical studies that had been submitted to the district court (J.A. 30–72, 87–121, 131–135).

On May 31, 1971, the Commissioner issued an order denying Hynson's request for a hearing and withdrawing approval of the NDA for Lutrexin (J.A. 72–78). The Commissioner held that Lutrexin was not exempt under Section 107(c)(4) because the NDA for Lutrexin had not been withdrawn prior to the enactment date of the 1962 amendments and was therefore

deemed approved thereunder (J.A. 74). The Commissioner further ruled that the new regulations governed Hynson's request for a hearing, and that Hynson had failed to satisfy the requirements of those regulations (J.A. 73–74). Turning to the substance of the submission, the Commissioner found that Hynson had not presented adequate and well-controlled clinical investigations in support of either its claim that Lutrexin is not presently a new drug or its claim that substantial evidence of effectiveness exists (J.A. 74, 77–78). He pointed out that, for the most part, Hynson had merely resubmitted a list of material previously submitted, that it had failed to point out what in the material was relevant, and that in any event the material "reveals a lack of adequate and well-controlled investigations showing that lututrin will have the effect HW&D claims for it" (J.A. 78). In a detailed review of Hynson's documentation, he demonstrated how each study showed deficiencies on its face that prevented it, under the rules, from being treated as an adequate and well-controlled study (J.A. 74–78).

On petition for review, the court of appeals reversed the Commissioner's withdrawal order (J.A. 181). While the court agreed with the Commissioner that Hynson's drugs were not exempt under Section 107 (c)(4) (J.A. 176–177),[8] it disagreed with his conclusion that Hynson was not entitled to a hearing on

[8] The court held that the exemption issue was one for the district court, not the agency, but, citing its opinion in *USV Pharmaceutical Corp.* v. *Richardson*, 461 F. 2d 223 (C.A. 4), it concluded that Hynson was not entitled to the exemption (J.A. 176). While ruling that only the district court could determine whether Hynson's product is currently a new drug,

the substantial evidence question. The court purported not to question the Commissioner's right to adopt regulations allowing denial of a hearing where no genuine substantial issue of fact is presented, and it presumed, without explicitly deciding, that this case is governed by the rules regarding availability of hearings that were in effect at the time of decision rather than those in effect at the time of Hynson's initial request for a hearing (J.A. 177).

Nonetheless, the court held that Hynson's submission had presented "'genuine and substantial' evidence that supports the position of the applicant" (J.A. 178). The court relied upon several factors: the "possibly effective" rating given the drug by the NAS-NRC panel; the absence of any record evidence of ineffectiveness; studies and opinions of medical experts of impressive credentials; and the affidavit of a former FDA medical officer that in his opinion Hynson had submitted adequate and well-controlled clinical investigations (J.A. 179–180). The Commissioner's efforts to demonstrate that deficiencies in Hynson's evidence made it inadequate under the statutory requirement for "adequate and well-controlled" studies were held to be unavailing. Such questions, the court stated, are to be resolved in an adversary hearing (J.A. 180).

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the court of appeals did not take issue on the merits with the Commissioner's holding that Lutrexin is a new drug (J.A. 176–177). The issue of FDA's right to decide this question is presented in *Hynson, Westcott and Dunning* v. *Weinberger*, No. 72–414, in *CIBA Corporation* v. *Weinberger*, No. 72–528, and in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72–555.

SUMMARY OF ARGUMENT

In enacting the 1962 amendments to the Federal Food, Drug, and Cosmetic Act of 1938, Congress mandated for the first time that drugs sold to the American public must be shown to be effective for their recommended use as well as safe. It made this requirement applicable not only to new drugs coming on the market after 1962, but also to drugs that were covered by NDAs that had become effective between 1938 and 1962. Moreover, prompted by the testimony of numerous prominent experts in medicine and pharmacology, Congress adopted a rigorous standard for the kind of evidence that could be considered in support of a drug's efficacy claims, requiring "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved * * *." Uncontrolled studies and anecdotal reports and testimonials of practitioners based upon their experiences were rejected as unreliable evidence of efficacy.

FDA's implementing regulations spell out in detail the kinds of studies that are considered to be "adequate and well-controlled investigations" eligible to support drug efficacy claims. They further provide that a manufacturer seeking a hearing in connection with a proposed withdrawal of approval for an NDA must show that he is prepared to present evidence at the hearing consisting of "adequate and well-controlled investigations" as defined in the regulations; otherwise his request for a hearing will be denied.

Since claims not bottomed on evidence of this sort cannot be accepted under the clear statutory directive, the holding of a hearing in the absence of a threshold showing that such evidence may exist would be futile and is not required. *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192; *Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33.

The court of appeals committed two fundamental errors in ordering a hearing before the Lutrexin NDA could be withdrawn. First, it based its decision on a variety of factors—such as testimonials of physicians based upon their personal experience; the "possibly effective" rating given to the drug by the NAS-NRC review panel; and the absence of proof of ineffectiveness—none of which is, under the statute and regulations, the kind of evidence that could support a claim of effectiveness. If, notwithstanding the statutory "substantial evidence" requirement, FDA is to be obliged to hold hearings on the basis of such evidence (which is of a kind that any manufacturer can produce for virtually any product that has been on the market for a period of years), the agency will be mired in pointless hearings for years and will be frustrated in its efforts to carry out the congressional mandate to remove from the market drugs whose efficacy claims are not supported by scientifically sound evidence of effectiveness.

The second error of the court of appeals was the application of an improper standard of review to the Commissioner's determination that the studies submitted by Hynson with its request for a hearing failed on their face to qualify under the regulations as "adequate and well-controlled investigations." The Commissioner's order withdrawing approval of the Lutrexin NDA carefully evaluated each item submitted by the manufacturer and showed why it could not qualify. The court of appeals did not find that any of the Commissioner's conclusions were unreasonable, erroneous, or arbitrary, but simply ordered a hearing because something might come out at such a hearing that would show that the studies were not as defective as they appeared to be on their face. In so ruling, the court did not accord the proper deference to the Commissioner's expert determination that Hynson had failed to meet its burden of coming forward with a threshold showing that evidence existed warranting a hearing. By failing to respect the Commissioner's judgment in this highly technical area, even though it has not found the judgment to be unreasonable, the court has translated the statutory requirement to provide an opportunity for hearing into a mandate for the holding of numerous time-consuming, needless hearings that would greatly impede the agency's program to remove ineffective drugs from the market.

496-754—73——3

ARGUMENT

I. THE FOOD AND DRUG ADMINISTRATION'S PROCEDURAL REGULATIONS PROPERLY IMPLEMENT SECTIONS 505(d) AND 505(e) OF THE ACT

A. THE STATUTE AND THE REGULATIONS ARE DESIGNED TO PROTECT THE PUBLIC BY IMPOSING EXACTING STANDARDS ON DRUG MANUFACTURERS TO SHOW THE EFFECTIVENESS OF THEIR PRODUCTS

The 1962 amendments to the Federal Food, Drug, and Cosmetic Act of 1938 are a landmark of American health legislation. They required for the first time that drugs sold to the American public be proven to be not only safe, but also effective, for their intended uses. As the House report on the legislation emphasized, the bill's purpose "better to protect the public health" was advanced by provisions requiring "that new drugs be shown to be effective as well as safe" and authorizing the "[w]ithdrawal of new drugs when their safety or effectiveness is no longer assured." H. Rep. No. 2464, 87th Cong., 2d Sess., pp. 1, 2.

Section 505(e) of the Act directs the Commissioner to refuse to approve a new drug application, or to withdraw approval of a new drug application previously approved, if the manufacturer fails to carry its burden of showing that there is "substantial evidence that the drug will have the effect it purports or is represented to have * * *." And further to "insure the reliability of drugs,"* Congress defined "substantial evidence" precisely and narrowly in Sec-

* S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess., p. 1.

tion 505(d) as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved * * *."[10]

The legislative history shows that the choice of this exacting standard was the result of a heightened congressional awareness that adequate and well-controlled clinical investigations are essential to determine drug effectiveness. As originally introduced by Senator Kefauver, the legislation would simply have added to existing Sections 505(d) and 505(e) of the Act the requirement that the drug be "efficacious in use," without providing a standard for measuring efficacy. S. 1552, 87th Cong., 1st Sess., Sec. 4(A)(9). However, hearings on the bill produced testimony from eminent physicians that anecdotal, uncontrolled evidence was not reliable, and that controlled clinical testing was necessary to make an adequate determination of drug effectiveness. As Dr. May, Professor of Pediatrics at New York University, succinctly stated: "A collection of impressions will not furnish the truth—this approach did not prevent doctors from having unbounded faith in the curative powers of leeches for hundreds of years before scientific evaluation became the preferred means of judging efficacy of therapy."[11]

[10] The same standard of "substantial evidence" is made applicable to antibiotic drugs by Section 507(h) of the Act (21 U.S.C. 357(h)).

[11] Hearings before the Subcommittee on Antitrust and Monopoly, Senate Committee on the Judiciary, on Drug Industry An-

Accordingly, when the Judiciary Committee reported the bill to the Senate in July 1962, it included provisions authorizing the Secretary to refuse to permit an NDA to become effective or to suspend the effectiveness of an NDA if "there is a lack of substantial evidence (including substantial clinical evidence), supported by investigations of experts qualified by scientific training and experience to evaluate the effectiveness of drugs, that the drug will have the effect it purports or is represented to have * * *." S. Rep. No. 1744, Part 1, 87th Cong., 2d Sess., pp. 25–26. And the Committee explained that "therapeutic claims for new drugs [must] be supported by reliable pharmacological and clinical studies." *Id.* at 16.

Before the Senate could act, however, the Judiciary Committee met again and reported new, stronger amendments.[12] Speaking of the language which became Section 505(d)'s definition of "substantial evidence," the Committee stated that it "clarifies and strengthens the previously reported bill by restating

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titrust Act, 87th Cong., 1st Sess., Part 1, p. 195 ("Hearings").

Other distinguished witnesses confirmed these remarks. See, *e.g.*, Hearings at 282, where Dr. Lasagna emphasized the importance of double-blind studies, and at 411–412, where Dr. Dowling spoke of the importance of placebo effect and of elimination of bias in selection and testing of patients. See *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301, 307–308 (D. Del.), for a further review of the legislative history underlying adoption of the definition of "substantial evidence."

[12] The impetus for the new consideration came from public concern over the thalidomide incident and pressure from the President for stronger legislation. S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess., p. 1.

and carefully defining the quality and quantum of evidence which the Secretary must find to exist as a basis for clearance of the drug or for withdrawal of a previously approved new-drug application." S. Rep. No. 1744, Part 2, *supra*, at p. 6. The Committee explained that "* * * a claim could be rejected if it were found (a) that the investigations were not 'adequate'; (b) that they were not 'well controlled'; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which the application is made; or (d) that the conclusions drawn by such experts could not fairly and responsibly be derived from their investigations." *Ibid.* Thus the history of the "substantial evidence" provisions of the Act shows increasingly stringent statutory language culminating in the provision that is now the law.

Since Congress insisted that "substantial evidence" consist only of "adequate and well-controlled investigations," FDA promulgated regulations defining the form such investigations should take. The need for these regulations became particularly clear in light of the experience of the NAS–NRC Drug Efficacy Study Group, which at the conclusion of its efforts in 1969 informed the Commissioner that "[t]he lack of substantial evidence based on well-controlled investigations by experienced investigators was conspicuous." NAS–NRC Report, p. 13.

The agency's carefully drawn regulations express well-established principles of scientific investigation, many of which were specifically referred to by doctors in congressional hearings on the 1962 Drug Amend-

ments. 35 Fed. Reg. 7250. Thus, the regulations require a clear statement of the objectives of the study and a method of subject selection and assignment to test groups that assures their suitability for the purposes of the study, minimizes bias, and assures comparability of pertinent variables such as patient age and disease severity. The researcher must explain the methods of observing and recording results. There must be an unbiased comparison with control groups under one or more of the following types of control: no treatment, placebo, active treatment, and historical. There must also be a statistically valid summary of methods and evaluation of results. While uncontrolled or partially controlled studies are unacceptable as the sole basis for approval of claims of effectiveness, they may, if carefully conducted and documented, be used to corroborate well-controlled studies. On the other hand, random experience, isolated case reports, and reports lacking the details which permit scientific evaluation will not be considered. The regulations also provide for waiver of any of the criteria upon a request and showing by a manufacturer that they are not reasonably applicable (J.A. 489).

Just as the NAS–NRC Study had alerted the Commissioner to the existence of large numbers of drugs for which there was a lack of substantial evidence of effectiveness, it had at the same time pointed up the need to develop procedures by which the agency could expeditiously carry out its duty of removing such drugs from the market. The study had covered approximately 4,000 drug products for which NDAs had

been obtained between 1938 and 1962. NAS–NRC Report, p. 5. Many of these products have been offered to the public for use in the treatment of more than one condition, so that, altogether, the NAS–NRC panels evaluated approximately 16,500 claims made on behalf of these 4,000 products. About 70 percent of these claims were found not to be supported by substantial evidence of effectiveness.[11] Indeed, only 434 drug products were found effective for all their claimed uses, leaving more than 3,500 as to which withdrawal of approval with respect to at least one claim is in prospect. If FDA were obliged to grant hearings on demand before withdrawing approval for each of these products, the agency would be mired in hearings for years, and it is difficult to see how or when the agency would be able to complete its fundamental task under the 1962 amendments of removing drugs of unproved effectiveness from the market.

FDA accommodated its responsibility to remove ineffective drugs from the market with its obligation under Section 505(e) to grant manufacturers an "opportunity for hearing" by adopting regulations re-

[11] See Hearings before the Subcommittee on Monopoly of the Senate Select Committee on Small Business on Competitive Problems in the Drug Industry, 92d Cong., 1st Sess., Part 20, pp. 7975–7976. The distribution of these claims among the various rating categories used by NAS–NRC was as follows: Ineffective—14.7%; possibly effective—35%; probably effective—7.3%; effective "but"—24%; effective—19.1%. The figure quoted in the text results from a redistribution of the "effective 'but'" group into the other categories. The meaning of the various categories utilized for rating purposes by the NAS–NRC panels is explained in the NAS–NRC Report, pp. 42–43. See also pp. 28–29, *infra*.

quiring the manufacturer to submit studies apparently constituting adequate and well-controlled investigations as defined in the regulations in order to obtain a hearing on the proposed withdrawal of an NDA (J.A. 490–491).[14] The manufacturer must submit an analysis of the data which he is prepared to prove at the hearing, and he must set forth specific facts "showing that there is a genuine and substantial issue of fact that requires a hearing" (J.A. 491).[15] If it clearly appears that there is no such issue of fact—for example, that adequate and well-controlled clinical investigations have not been identified in support of the claims of effectiveness—the Commissioner will then enter an order, with appropriate findings and conclusions, withdrawing approval of the NDA (J.A. 491). That is what occurred in the instant case, and, we submit, respondent was thereby afforded the "opportunity for hearing" required by Section 505(e) of the Federal Food, Drug, and Cosmetic Act, *supra*. It is a disposition similar in some respects to a trial court's granting of a motion for summary judgment when there

[14] Substantially the same regulations apply to proceedings for removal of ineffective antibiotics from the market. See 21 C.F.R. 146.1(d).

[15] The nature of the problem is such that formal hearings are not likely to be needed in many instances. If studies exist that appear on their face to constitute adequate and well-controlled investigations as defined in the regulations, the Commissioner would, in the absence of unusual circumstances, find the drug effective and not pursue withdrawal of its NDA. If the manufacturer is unable to make a *prima facie* showing that such studies exist, a hearing would be useless.

are no legally relevant controverted facts to be decided or to the granting of a motion to dismiss a complaint for failure to state a claim on which relief can be granted. In this sense, the applicant has had full opportunity to make his basic case and has been heard, and, as we explain *infra* (pp. 33–35), the agency's denial under its regulations of a fuller hearing on the facts of this case is subject to appropriate judicial review.

B. THE REGULATIONS ARE VALID

The regulations defining what constitutes "adequate and well-controlled investigations" conforming to the statutory requirement have been upheld whenever challenged in the past. *Upjohn Co.* v. *Finch*, 422 F. 2d 944 (C.A. 6); *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del.). Their validity is not at issue in this case.

Nor has either side petitioned this Court to review the conclusion of the court of appeals that the regulations conditioning the availability of a hearing on the establishment of a genuine and substantial issue of fact (by specifying the existence of adequate and well-controlled clinical investigations) are valid on their face. The only mention of this issue came in Hynson's Brief in Opposition, filed after the 90-day period for petitioning for certiorari had expired, wherein Hynson stated that, if the government's petition were granted, it "would want to place * * * before this court" the question of the validity of the regulation (Br. in Opp., p. 3). There is thus some

doubt whether the issue is properly before this Court. Since, however, it could be argued that invalidation of the regulation on availability of hearings would constitute an alternative ground for affirmance of the judgment below, we discuss this question here and contend that the regulation is valid.

The procedural regulation governing the right to a hearing dovetails with the substantive regulations defining what can be considered "adequate and well-controlled investigations," the statutory precondition to a finding that "substantial evidence" of effectiveness exists. It reflects a "threshold requirement" for a hearing. *American Cyanamid Co.* v. *Richardson*, 456 F. 2d 509, 513 (C.A. 1).[16] The regulation does no more than place upon the party demanding a hearing the responsibility to present "the evidence needed to make out a *prima facie* case." *Ciba-Geigy Corp.* v. *Richardson*, 446 F. 2d 466, 468 (C.A. 2). A hearing would be a time-consuming and useless formality unless the manufacturer is prepared to present evidence of the precise type that is required by statute and valid regulation thereunder to support a claim of effectiveness.

Thus, the regulations work in a manner closely akin to those upheld by this Court in *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192, where the Federal Communications Commission, relying on its newly promulgated regulation limiting one person to ownership of five television stations, dismissed without hearing Storer's application for a sixth station. This

[16] The *American Cyanamid* decision was by Judge Coffin alone, denying a motion for stay of an order of withdrawal.

Court affirmed the Commission's regulation and its action thereunder as consistent with the hearing provision of Section 309(b) of the Communications Act, observing that Congress had not "intended the Commission to waste time on applications that do not state a valid basis for a hearing." *Id.* at 205. Similarly, in *Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33, 39, the Court dealt with a situation precisely parallel to that here:

> * * * [T]he statutory requirement for a hearing under § 7 does not preclude the Commission from particularizing statutory standards through the rulemaking process and barring at the threshold those who neither measure up to them nor show reasons why in the public interest the rule should be waived.

The courts of appeals have similarly declined to insist upon the holding of hearings when there are no material issues of fact to be resolved. See, *e.g.*, *Municipal Light Boards* v. *Federal Power Commission*, 450 F. 2d 1341, 1345 (C.A.D.C.); *Citizens for Allegan County* v. *Federal Power Commission*, 414 F. 2d 1125, 1128 and n. 5 (C.A.D.C.); *Virginia Electric and Power Co.* v. *Federal Power Commission*, 351 F. 2d 408, 410 (C.A. 4). Moreover, the Administrative Conference of the United States has recommended that all agencies adopt rules for summary decision, 38 U.S.L.W. 2658, and several other agencies currently have similar rules dispensing with a hearing when there is no genuine issue of fact to be determined. See, *e.g.*, 16 C.F.R. 3.24 (Federal Trade Commission); 29 C.F.R. 102.24 (National Labor Relations Board).

Applying these principles to the present situation, if a manufacturer is not prepared to present data derived from the kind of adequate and well-controlled investigations required by the statute and FDA regulations, a hearing would be as much a waste of time as in *Storer* or *Texaco*. It is not surprising, then, that every court that has ruled on the question, including the court of appeals in the instant case, has upheld the lawfulness of the Commissioner's regulations (J.A. 177; *Ciba-Geigy Corp.* v. *Richardson*, 446 F. 2d 466 (C.A. 2); *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del.); *Upjohn Co.* v. *Finch*, 422 F. 2d 944 (C.A. 6); *Pfizer, Inc.* v. *Richardson*, 434 F. 2d 536 (C.A. 2)). It is thus clear that the regulations conform to the statute and to administrative due process.[17]

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[17] Hynson has also indicated in its Brief in Opposition (p. 8) that it will seek to argue the question whether it was entitled to a hearing because its original hearing demand preceded adoption of the "summary judgment" regulations. This question too was not presented in either certiorari petition in this case. It is, in any event, an unmeritorious contention. Since Hynson has never had adequate and well-controlled clinical investigations substantiating the efficacy of Lutrexin, there has never been anything to be determined in an adjudicatory hearing. The change in FDA's procedural regulations merely made explicit what had previously been implicit—that FDA need not hold a hearing if there are no material issues of fact to be determined.

In any event, *Storer* is dispositive of this contention, since the Court there held lawful the five-station regulations and their applicability to *Storer* although the Commission had issued them after Storer had filed its application for a sixth station (351 U.S. at 205). Similarly, here the Commissioner had the right to make the May 1970 regulations applicable to all

II. THE COURT OF APPEALS ERRED IN HOLDING THAT THE COMMISSIONER IMPROPERLY DENIED HYNSON A HEARING

The Commissioner denied Hynson's request for a hearing because it clearly appeared from examination of the data submitted that none of the studies upon which Hynson relied were adequate and well-controlled clinical investigations as required by the regulations (J.A. 74, 78). The court of appeals reversed, holding that the Commissioner's objections "* * * do not justify a final conclusion, made *ex parte*, without a hearing, that it 'clearly appears' that there is no genuine issue of fact on the effectiveness of Lutrexin * * *" (J.A. 180). We believe that the court of appeals seriously misconstrued the meaning of the regulations whose validity it upheld and did not give proper weight to the determination of the Commissioner.

A. THE COURT OF APPEALS FAILED TO APPRECIATE THE HIGHLY PARTICULARIZED SHOWING OF SUBSTANTIAL EVIDENCE OF EFFECTIVENESS REQUIRED BY THE STATUTE AND THE REGULATIONS

Section 505(e) of the Act requires the withdrawal of the NDA of any drug when "there is a lack of substantial evidence" of the drug's effectiveness. Sec-

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persons as to whom NDA withdrawal proceedings were then pending. In *Upjohn*, *supra*, the court of appeals upheld agency action denying Upjohn a hearing on September 19, 1969, on the basis of regulations promulgated that very day. And see, generally, *Thorpe* v. *Housing Authority*, 393 U.S. 268, 281–283.

tion 505(d) defines "substantial evidence" to mean "adequate and well-controlled investigations, including clinical investigations, by experts" which enable experts to conclude that the drug will have the effect claimed for it. And FDA's regulations spell out with particularity what kinds of clinical investigations are adequate and well-controlled. Thus the holder of an NDA must show the effectiveness of his drug by the kind of clinical investigations that the statute and the regulations demand, and this substantive requirement shapes the procedural issue of what a manufacturer must show in order to gain a hearing. He must, by the data he submits, make at least a "threshold"[18] or "*prima facie*"[19] showing that his evidence is of the precise type the statute and regulations require. If he fails in that showing, he has failed to establish that there is any legally relevant issue of fact meriting a hearing, and in such circumstances a hearing would be a waste of time. *Storer Broadcasting, supra,* 351 U.S. at 205.

The court of appeals, however, did not appreciate this linkage between the substantive standards for effectiveness and the procedural requirements for a hearing. The court stated that the issue before the Commissioner was "the effectiveness of Lutrexin" (J.A. 180). This is too broad and imprecise a formulation of the relevant issue. The issue on the request for a hearing is not generally the "effectiveness" of the drug, but, much more narrowly, whether there is a

[18] *American Cyanamid, supra,* 456 F.2d at 513.

[19] *Ciba-Geigy Corp., supra,* 446 F.2d at 468.

showing of substantial evidence of effectiveness defined the way the statute and the regulations define it. Since Congress has directed that only adequate and well-controlled clinical investigations will qualify as substantial evidence of a drug's effectiveness, and the Commissioner's regulations properly give content to the congressional standard, evidence of that kind must be presented to get a hearing.

As a result of this misunderstanding, the court held relevant to the issue of a hearing various criteria which have no relevance to the critical question whether the manufacturer can produce substantial evidence of the necessary kind:

1. Thus, the court noted that no qualified expert had stated that Lutrexin was ineffective for its intended uses (J.A. 179). But this is doubly irrelevant: the statute and the regulations do not require FDA to prove a drug ineffective, but rather oblige the manufacturer to show substantial evidence of effectiveness. See *Ubiotica Corp.* v. *Food and Drug Administration,* 427 F.2d 376, 378 (C.A. 6). Moreover, the manufacturer must show effectiveness by very specifically defined "substantial evidence," and absence of expert condemnation of a drug as ineffective in no way meets the substantial evidence requirements of the Act and the regulations.

Indeed, Congress has in one respect been lenient in establishing the burden of proof of efficacy that the manufacturer must shoulder. He need not prove that the drug is effective beyond a reasonable doubt or even by a preponderance of the evidence. As stated in

the NAS–NRC Report (p. 8), "claims for effectiveness should be accepted if a substantial amount of well-documented favorable evidence is presented, even though there may also exist a weighty body of inconclusive or negative evidence." See also S. Rep. No. 1744, Part 2, *supra*, at p. 6. FDA has never sought to impose a weightier burden. But where the manufacturer is, as here, unable to point to *any* evidence of the necessary quality, there is no point in launching an inquiry whether a "substantial" quantum of such evidence exists.

2. Similarly, the court of appeals' reference to the "possibly effective" rating given Lutrexin by the NAS–NRC review panel misses the mark—all the more so in view of the fact that the panel pointedly noted the manufacturer's failure to produce well-controlled studies (J.A. 7). A "possibly effective" rating, far from constituting substantial evidence of effectiveness as defined by the statute and regulations, instead reflects a lack of such evidence in support of the drug. Cf. *American Public Health Assn.* v. *Veneman*, 349 F. Supp. 1311, 1314 (D.D.C.). The instructions to the panels directed use of the "possibly effective" rating in the following circumstances (NAS-NRC Report, p. 42):

> In relation to the indication in question, there is little evidence of effectiveness under any of the criteria stated above. The possibility that additional supporting evidence might be developed should not be ruled out, however. The recommendations to the FDA could be that unless it is informed that studies are being initiated

> promptly with the object of developing substantial evidence of effectiveness, the indication in question should be considered inappropriate.

The report observed that "[t]he definition [of substantial evidence] in the law is an exacting one. Had the panels adhered rigidly to it, a great many claims would have been rejected on the grounds that they were not supported by substantial evidence * * *" (*id.* at 8). It indicated that, in such circumstances, the intermediate ratings of "probably effective" and "possibly effective" were assigned "on the basis of [the panel members'] own clinical experience with the drug and their evaluation of the opinions of their peers" (*id.* at 9).

Nearly 6,000 of the 16,500 claims evaluated by NAS–NRC received "possibly effective" ratings (see n. 13, *supra,* and accompanying text), and if such a rating entitles the manufacturer to an evidentiary hearing, FDA would be obliged to hold hearings on thousands of claims with respect to which the manufacturer had not produced any evidence meeting the requirements of law.

3. The court evidently was also impressed that several physicians of high professional standing believe Lutrexin to be effective (J.A. 179). However, unless such views are premised on properly conducted investigations, they are not of significant probative value under the law. Manufacturers can almost always produce, as Hynson did (J.A. 29, 32–58), affidavits or testimonial letters from qualified physicians proclaiming their belief in the efficacy of the manufacturer's

product. But this is precisely the type of anecdotal evidence that Congress rejected as unreliable for the purposes of the 1962 amendments (see pp. 15–16, *supra*) and which the regulations rightly hold will not be considered in determining whether there is a lack of substantial evidence of efficacy (J.A. 490). If the agency were compelled to conduct a full evidentiary hearing in every case in which this type of proof is offered, decades might pass before it would be able to complete its fundamental task under the 1962 amendments of removing from the market drugs of unproved effectiveness.[20]

Thus, despite the court's professed intention to uphold the validity of the regulations, its reliance on evidence which is not "substantial" to direct a hearing effectively nullifies those regulations and renders implementation of the statute virtually impossible.

[20] Recognition of FDA's ability to withdraw approval of NDAs without an evidentiary hearing when the manufacturer is unable to make the threshold showing of the existence of studies that could constitute substantial evidence of effectiveness is particularly important in view of the fact that FDA is currently under court order to proceed with greater dispatch in evaluating the efficacy of drugs studied by NAS–NRC and removing from the market those not shown to be effective. *American Public Health Association* v. *Veneman*, 349 F. Supp. 1311 (D.D.C.). The court's order obliges the Commissioner, by October 10, 1976, to give notice of opportunity for hearing and to rule on all requests for hearing in connection with all such drugs not found by him to be effective. The agency is currently laboring to carry out the court's order punctually, but its efforts will be of little avail and of no benefit to the public if all that is accomplished is to bring nearer the holding of hundreds or thousands of pointless hearings.

B. THE COURT OF APPEALS ALSO ERRED IN REVERSING THE COMMISSIONER'S DETERMINATION THAT THE STUDIES WHICH HYNSON PRODUCED TO SUPPORT ITS CLAIM FOR A HEARING WERE NOT ADEQUATE AND WELL-CONTROLLED CLINICAL INVESTIGATIONS AS DEFINED BY THE REGULATIONS.

1. The Court of Appeals Applied an Erroneous Standard of Review.

The court of appeals, as we have pointed out in the preceding section, erroneously considered irrelevant factors in deciding that Hynson was entitled to a hearing. The court also applied an erroneous standard of law to the Commissioner's appraisal of those studies which Hynson did send him that were claimed to be in conformity with the procedural regulations.

After losing its district court suit against the Commissioner (J.A. 23–24), Hynson submitted data to FDA which it claimed to be substantial evidence within the meaning of the regulations and to be sufficient to warrant a hearing (J.A. 27–32). By then, Hynson had had eight years from the enactment of the 1962 amendments within which to develop the kind of substantial evidence of effectiveness required by the Act (the two-year statutory grace period provided by Section 107(c)(3) of the 1962 legislation and six additional years). Although the regulations required an applicant to provide "a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove" (J.A. 491), Hynson sent the Commissioner a heterogeneous and unorganized mass

of documents ranging from testimonial letters to court pleadings (see J.A. 27–32).

From this material, the Commissioner culled the medical studies. Several of the studies were papers which Hynson had already sent to him in the past,[21] but he nonetheless examined them all in terms of the applicable substantial evidence regulations. He then gave a careful and well-reasoned explanation [22] of why Hynson had failed to present a threshold showing that its studies were adequate and well-controlled clinical investigations within the meaning of the substantial evidence regulations (J.A. 74–78). Hynson now admits that many of those studies "do not pur-

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[21] For example, Hynson had first sent the Commissioner the papers by Gratton (J.A. 87–92), Gray (J.A. 131–135), and Majewski (J.A. 106–111) in 1968 (J.A. 28).

[22] Because the Commissioner's order was thorough and reasoned, it does not suffer from the lack of findings which the court of appeals held grounds for reversal in *USV Pharmaceutical Corp.* v. *Secretary of Health, Education, and Welfare*, 466 F. 2d 455, 461–462 (C.A.D.C.), a decision in proceedings related to those involved in No. 72–666. The *USV* decision, *supra*, also holds that the Commissioner may not simply rely on the reports of the NAS–NRC panels to call upon the holder of an NDA issued prior to October 10, 1962, to produce evidence of effectiveness establishing his right to a hearing or lose approval of the NDA. *Id.* at 461. We disagree. Congress wanted to make sure that drugs were effective: both those that had come on the market before 1962 and those that came on after 1962. In furtherance of that statutory purpose, the Commissioner may, by adopting the findings of the NAS–NRC panels, rightly place upon the holder of NDAs issued prior to October 10, 1962 (when it was not necessary to submit any proof of effectiveness to receive approval of an NDA) the burden of coming forward with substantial evidence of effectiveness, to avoid withdrawal of the approval of that NDA.

port to be controlled studies" (Br. in Opp., No. 72–394, p. 13) and thus do not measure up to the regulations. The critical shortcoming of the others are, we submit, clearly and correctly exposed in the Commissioner's decision. See pp. 36–38, *infra*.

The court of appeals assumed for purposes of its decision the correctness of the Commissioner's critique of Hynson's studies, but it held that "at most" the critique only created an issue of fact on the adequacy of the studies to be resolved at a hearing (J.A. 180). Although the court's reasoning is not free from ambiguity, it appears to rest on the premise that a hearing is necessary so long as there remains a possibility that some evidence of the necessary kind will turn up at the hearing, even if the Commissioner has reasonably determined that the manufacturer has at the threshold stage failed to produce any.[23] This reasoning misconceives the respective roles of agency and reviewing court and seriously undermines the regulations.

The Commissioner's determination that a manufacturer has failed to make even a threshold showing of the existence of studies that could qualify as "substantial evidence" is, to be sure, subject to judicial review. Such a determination, however, involving the appraisal of technical medical studies in light of the

[23] It is possible that the court of appeals meant to hold that a hearing is necessary before the Commissioner may determine whether a manufacturer has made a threshold showing of "substantial evidence" as required by the regulations. But this would require a hearing in every case and would thus be inconsistent with the court's professed belief in the validity of the procedural regulations (J.A. 177).

standards of the regulations, necessarily requires to a high degree the use of expertise particularly within the province of FDA and notably not the strength of courts. See, *e.g.*, *United States* v. *Bacto-Unidisk*, 394 U.S. 784, 791–792. As Judge Friendly observed in a decision upholding a similar determination of the Commissioner to deny a requested hearing: "* * * such a determination is peculiarly within the FDA's expertise and we would be reluctant to intrude into medical matters we do not truly understand * * *." *Pfizer, supra,* 434 F. 2d at 546.[24] This, of course, does not mean that the courts are to abdicate their reviewing function, but it does mean they should perform that function with awareness of the respective competencies of court and agency. A reviewing court should determine whether the Commissioner has articulated the grounds of his decision, whether they are consistent with the statute, and whether they are supported by the evidence. In short, if the Commissioner's decision shows "that the FDA had a reasonable basis for considering that * * * [the manufacturer's] submissions did not comply with the requirement of the statute, and the Regulation" (*id.* at 547), the court should affirm.

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[24] In *Pfizer*, as in the present case, the manufacturer submitted studies which it claimed were adequate and well-controlled clinical investigations showing the efficacy of its drug (an antibiotic) and entitling it to a hearing. The Commissioner reviewed the studies, pointed out their deficiencies, and denied a hearing. 434 F. 2d at 546–547. In *Upjohn*, *supra*, the same contention was made by the manufacturer, who had submitted 54 documents in support thereof, and was rejected by the Commissioner and the court (422 F. 2d at 951).

The decision of the court below, by contrast, requires of the Commissioner more than articulate reasonableness: it requires the exclusion of any possibility that a hearing might result in production of substantial evidence of effectiveness. And, expert as the Commissioner is, this is a burden that he should not be expected to carry. It is possible that, in some rare instances, a hearing would produce new information justifying a different conclusion about a given question. In some situations, but not here, one could not automatically rule out the possibility that examination of the authors and the reliability of their investigations, as suggested by the court of appeals (J.A. 180), might ultimately show that their studies met the requirements of the regulations. But there is no obligation on the Commissioner, after he has made a reasonable determination that the studies fail to conform to the regulations, to negative the almost endless, if remote, possibilities that a hearing might still turn up relevant evidence. Surely neither the statute nor the regulations require the Commissioner to hold a hearing on the basis of such speculative possibilities. For to require a hearing in such circumstances would in effect be to require a hearing in every case, and the Commissioner's procedural regulations, though never formally struck down, would be as ineffective as if invalidated.

2. *The Commissioner Properly Determined That the Studies Submitted by Hynson Do Not Meet the Requirements of the Regulations.*

Under a proper standard of review, the court of appeals should have ruled that the Commissioner correctly denied Hynson's request for a hearing. Hynson submitted (or referred the Commissioner to) a pair of studies written in the 1950's by Rezek (J.A. 112–121), four papers by Trythall (J.A. 135–148),[25] and articles by Gray (J.A. 131–135), G. Jones and Smith (J.A. 160–167), and S. Jones (J.A. 167–171). Since Hynson now concedes that these "do not purport to be controlled studies" (Br. in Opp., No. 72–394, p. 13), there is no need to rehearse the Commissioner's findings that these studies failed to conform to the regulations (J.A. 76–78).

Hynson also submitted to the Commissioner two papers written in the mid-1950's reporting on a study by Majewski and Jennings (J.A. 92–105), who concluded that "Lutrexin is successful in controlling uterine contractions * * *" (J.A. 105). As the Commissioner explained, severe deficiencies in the study prevent it from meeting the standards of the regulations. For example, the authors admitted that some patients had received medication in addition to Lutrexin (J.A. 97, 101). As the Commissioner properly observed, "[t]here is no way to determine the percentage of patients on concurrent medication or whether the results of the study were thereby influenced" (J.A. 75). By not stating what other drugs they used, in what amounts, and to whom they were administered, Majewski and Jennings plainly failed to meet the requirement of the regulations that the study's plan and re-

[25] Two of the Trythall papers are not printed in the Joint Appendix.

port "* * * must include * * * (2) A method of selection of the subjects that * * * (iii) Assures comparability in test and control groups of pertinent variables, such as * * * use of drugs other than the test drug" (J.A. 487–488). Similarly, the authors, although freely using statistics, did not give a summary or explanation of their statistical methodology and thus failed to conform to the requirement of the regulations that there must be a summary of methods, "including any appropriate statistical methods" (J.A. 489).[25]

Hynson also submitted an unpublished article written in 1968 by Gratton, who reported good results with Lutrexin in the treatment of prematurity (J.A. 87–92) in patients who were claimed to have served as their own controls (J.A. 89). Even if this method of control were acceptable, the study does not meet the requirements of the regulations (J.A. 487–488) because the use of numerous medications concurrently makes impossible a scientific attribution of the results to Lutrexin; the method of selecting patients, who were not shown to be representative of the population about which inferences were made, is not explained; and the pairing of different patient groups lacked adequate statistical design and evaluation.

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[25] Without reasoned explanation of the statistical methods, it is not possible to tell whether the results in the test group were due to chance or to some kind of bias (J.A. 75). Statistical infirmities, ranging from inadequate definition of the subject population to inaccurate comparisons of patients within the test group (J.A. 75–76), also mark Majewski's unpublished 1968 paper (J.A. 106–111).

The deficiencies of Hynson's studies, as elucidated by the Commissioner, thus justify his determination that none of the studies are adequate and well-controlled clinical investigations within the meaning of the regulations." We need not speculate on what the results of the proceedings might have been had Hynson requested a waiver of the criteria of the regulations, as it had a right to do (J.A. 489), since Hynson never requested a waiver.

Nor, contrary to the opinion below (J.A. 180), is the Commissioner's decision vitiated by the affidavit of Dr. Sadusk, which Hynson submitted (J.A. 58-59). Although the court states that the Commissioner "disregards the categorical opinion of his former Director of the Bureau of Medicine and Medical Director [Dr. Sadusk][28] that the clinical tests and investigations submitted by the appellant [sic] represented '"well-controlled" clinical studies'" (J.A. 180), this is erroneous in two respects. First, the Commissioner did not disregard the views of Dr. Sadusk. See J.A. 77. Second, Dr. Sadusk never stated that the studies which Hynson submitted were well-controlled. Indeed, Dr. Sadusk's affidavit does not even mention Hynson's

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[27] Contrary to Hynson's suggestion (Br. in Opp., No. 72-394, pp. 10-12), the fact that one of the studies sought to use historical controls was not the reason for the Commissioner's rejection of it. The regulations make provisions for the use of historical controls (J.A. 488-489). Rather, the Commissioner's criticism was that the author's use of historical control was inadequate (J.A. 77).

[28] Dr. Sadusk left the employ of the Food and Drug Administration in 1967 and at the time of his affidavit (January 22, 1970) was a vice-president of Parke, Davis & Company, a large pharmaceutical manufacturer (J.A. 59-63).

studies—all of which were written well before his affidavit—and, for all the affidavit states, he never even saw them.

What the affidavit does say is that double-blind studies or placebo controls may be unethical, immoral or illegal in certain cases, that cases involving threatened and habitual abortion and premature labor may be such cases, and that in such cases studies "based on statistics, or historical controls (including patient's own history) may well be expected to produce 'well controlled' results under the circumstances" (J.A. 59). But the Commissioner's regulations explicitly provide for historical controls, and for the right to seek a waiver even of that (J.A. 488–489). Hynson never sought a waiver, and the Commissioner's decision showed the serious flaws in the submitted studies, including their controls. Since it does not deal with those studies, the Sadusk affidavit in no way controverts the Commissioner's determination.[29]

Accordingly, the Commissioner's denial of Hynson's request for a hearing and his withdrawal of approval of the NDA for Lutrexin should have been upheld by the court of appeals.[30]

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[29] If the affidavit is read to mean that, in the absence of a waiver, there is no need for controls—even historical—then it is contrary to the regulations and irrelevant for that reason.

[30] Withdrawal of the NDA does not mean that Lutrexin is forever banished from the market. Hynson is at liberty to file for approval a new NDA for Lutrexin, either with new studies or with the same studies and a request for a waiver.

CONCLUSION

For the foregoing reasons, the judgment of the court of appeals should be reversed.

Respectfully submitted.

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 414

HYNSON, WESTCOTT & DUNNING, INCORPORATED,
Cross-petitioner,

v.

ELLIOT L. RICHARDSON, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs

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On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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BRIEF FOR CROSS-PETITIONER HYNSON, WESTCOTT & DUNNING, INCORPORATED

OPINIONS BELOW

The Opinion of the Court of Appeals (J.A. 173)[1] is reported at 461 F.2d 215. The Order of the Commissioner of Food and Drugs reviewed by the Court of Appeals was

[1] J.A. refers to the single joint appendix for the five cases consolidated by the Court's order of January 8, 1973.

published in the Federal Register of June 18, 1971 (36 F.R. 11,763, J.A. 72). The opinions in two related cases decided by the Fourth Circuit, *USV Pharmaceutical Corporation* v. *Richardson* (J.A. 466) and *Bentex Pharmaceuticals* v. *Richardson* (J.A. 258) are reported at 461 F.2d 223 and 463 F.2d 363 respectively. *Ciba Corporation* v. *Richardson*, a case consolidated by the Court with the instant case and *USV* and *Bentex*, is reported at 463 F.2d 225 (J.A. 215).

JURISDICTION

The Judgment of the Court of Appeals in the instant case (No. 414) was entered May 24, 1972. On August 17, 1972, Mr. Justice Rehnquist extended the time for filing a petition for writ of certiorari to and including September 11, 1972. The petition of the Solicitor General in No. 394 and the cross-petition in the instant case were granted on January 8, 1972. Petitions in the related cases of *Bentex*, *USV* and *Ciba* were also granted on that date.

The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1) and 21 U.S.C. 355(h).

STATUTES AND REGULATIONS INVOLVED

The pertinent statutory provisions are set forth in the Joint Appendix at p. 475 *et seq.* For convenience, excerpts from such provisions are hereinafter set forth.

Federal Food, Drug and Cosmetic Act, 52 Stat. 1040, as amended by the Drug Amendments of 1962, P.L. 87-781, (Harris-Kefauver Act), 21 U.S.C. 301 *et seq*:

Section 201(p)(1) and (2), 21 U.S.C. 321(p)(1) and (2):

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal

drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

Section 505, (a), (b), (e), 21 U.S.C. 355(a), (b), (e):

(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such person shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use. * * *

* * * *

(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this

section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof. * * *

Section 107(c) of Public Law 87-781, 76 Stat. 788-789, note following 21 U.S.C. 321 (1970 ed).

(1) As used in this subsection, the term "enactment date" means the date of enactment of this Act; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.

(2) An application filed pursuant to Section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

* * * *

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commer-

cially used or sold in the United States, (B) was not a new drug as defined by Section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under Section 505 of that Act, the amendments to Section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

QUESTIONS PRESENTED

The Questions involved in the instant case (No. 414) are not raised in the Government's petition in No. 394,[2] but were presented to the court below by cross-petitioner. The questions are:

(1) Whether the decision of the Court of Appeals was correct that the Commissioner of Food and Drugs was without authority to determine initially his own jurisdiction in a proceeding to withdraw a new drug application on the ground that there was a lack of substantial evidence of the subject drug's effectiveness, i.e., whether the drug is a "new drug" or, if it is a "new drug", whether it is exempt from the effectiveness requirements of the Drug Amendments of 1962.

(2) Whether one whose drug is the subject of such a withdrawal proceeding is entitled to an administrative hearing at which evidence may be introduced as a basis for deciding whether the Commissioner had jurisdiction to conduct such a proceeding.

(3) Whether a new drug application for a drug which had become generally recognized as safe on the day before

[2] The issue in No. 394 is whether Hynson, Westcott & Dunning was entitled to a hearing on the question of whether there was a lack of substantial evidence of effectiveness of Lutrexin (See Brief in Opposition to Petition for Writ of Certiorari in No. 394, p. 3.)

the effective date of the Drug Amendments of 1962 (October 9, 1962) was no longer an "effective" application within the meaning of Section 107(c)(2) of such amendments and therefore such application was not "deemed approved" under that section.

(4) Whether a drug which had become generally recognized as safe on the day before the effective date of the Drug Amendments of 1962 was a "new drug" on that date and was "covered by an effective application" within the meaning of Section 107(c)(4)(B) and (C) of such Amendments.

STATEMENT

Hynson, Westcott & Dunning, Incorporated (HW&D) has since 1953 marketed Lutrexin, a prescription drug, for use in the treatment of premature labor, second and third trimester threatened abortion, and dysmenorrhea (menstrual discomfort). The drug was, when first marketed in 1953, a "new drug" within the meaning of Section 201(p) (21 USC 321(p)), of the Federal Food, Drug and Cosmetic Act as then written (52 Stat. 1040, the "Act"). Pre-marketing clearance of Lutrexin under the new drug provisions of Section 505 of the Act, (21 USC 355) was, therefore, necessary, and a new drug application (NDA) for the drug was filed and became effective on December 23, 1953.

Until 1962 the test under Section 201(p)(1) for determining the necessity for obtaining pre-marketing clearance of a drug was whether the product was generally recognized as safe by qualified experts. Congress, in the Drug Amendments of 1962 (P.L. 87-781), amended Sections 201(p) and 505 of the Act to require pre-market clearance of new drugs for both safety and effectiveness. Thus, Section 201(p)(1), as amended, defined "new drugs" as those not generally recognized by qualified experts as both safe *and* effective for their intended uses.

Congress also, in 1962, added to Section 505(d) and (e) the concept of "substantial evidence of effectiveness," a concept separate and apart from the concept of general recognition of safety and effectiveness. The latter is solely a jurisdictional test to determine whether a drug is "new" under Section 201(p). The manufacturer of a product which was a new drug under the jurisdictional test, because of a lack of general recognition of effectiveness would, in order to obtain approval of an NDA for his product under amended Section 505, have to supply the Food and Drug Administration (FDA) with substantial evidence of the effectiveness of the drug. Likewise, where appropriate, FDA could, under Section 505(e)(3), withdraw approval of a new drug's NDA if it found a lack of substantial evidence of the drug's effectiveness.

A. Background

By notice published in the Federal Register of May 24, 1968, (J.A. 10) the Commissioner of Food and Drugs announced that FDA had reviewed and evaluated a report (J.A. 5) of the National Academy of Sciences-National Research Council (NAS-NRC) on Lutrexin;[3] that Lutrexin was found by the Academy to be "possibly effective"; that the claims made for the drug are inappropriate or unwarranted in the absence of sound documentation; and that the Food and Drug Administration had concluded the same thing. The notice offered HW&D the opportunity to submit documentation in support of the representations made for the products. HW&D submitted such data under date of November 22, 1968.

By notice published in the Federal Register of March 22, 1969, (J.A. 12) the Commissioner of Food and Drugs found that the additional data submitted by HW&D did not provide substantial evidence of the effectiveness of

[3] FDA had contracted with NAS-NRC to review the effectiveness of drugs cleared for marketing as "new drugs" between 1938 and 1962 on the basis of proof of safety only.

Lutrexin for its recommended uses. The notice offered HW&D an opportunity for a hearing "In accordance with the provisions of Section 505 of the Act (21 USC 355) and regulations promulgated thereunder (21 CFR Part 130)".

By letter to the hearing clerk of the FDA dated April 18, 1969, HW&D elected to avail itself of the opportunity for a hearing, reserving the right to contest the jurisdiction of the Commissioner and the Food and Drug Administration in the administrative proceedings, or in judicial proceedings, or in both (J.A. 14).

On August 19, 1969, HW&D filed a complaint for declaratory judgment and injunctive relief in the United States District Court for the District of Maryland (*Hynson, Westcott and Dunning, Incorporated* v. *Finch*, C.A. No. 21112), seeking a judicial determination of the status of Lutrexin under Sections 201(p) and 505 as amended in 1962 (J.A. 15).

After hearing in open court upon the Government's motion to dismiss, Judge Northrop, on September 16, 1970, dismissed the suit on the ground that the issues presented to the Court were within the primary jurisdiction of the FDA and that HW&D had failed to exhaust its administrative remedies. The order (J.A. 23) provided that HW&D's administrative remedies would enable it to "obtain an Agency determination on the record made before the Agency on the medical issues involved, on its claim that the drugs involved are generally recognized among qualified experts as safe and effective for their intended uses, its claim that they are protected from the drug efficacy review by the grandfather clause of the 1962 Amendments, and the claim that there is substantial evidence available to support the therapeutic effectiveness for which the drugs are promoted."[4]

[4] The claims of HW&D relating to "new drug" status and the grandfather provisions are sometimes referred to herein as "jurisdictional questions".

Pursuant to that order, by letter dated October 16, 1970, HW&D (J.A. 24), requested the Commissioner of Food and Drugs to reinstitute hearing procedures on the question of the proposal of FDA to withdraw the new drug application for Lutrexin, under Section 505(e) of the Act, and to grant HW&D a hearing on the jurisdictional questions, which the court had held were within the primary jurisdiction of the FDA. With that request, HW&D submitted the affidavits of expert physicians, and supporting medical data, which had been filed with the court in the Maryland litigation. By notice (order) published in the Federal Register of June 18, 1971, the Commissioner of Food and Drugs denied HW&D a hearing on any of the questions involved and withdrew "approval" of the new drug application (J.A. 72).

B. Decision Of The Court Of Appeals

The Court of Appeals held that HW&D was entitled to a hearing on the question of whether there is a lack of substantial evidence of the effectiveness of Lutrexin.[5] In addition to this point, four basic questions were before the Court of Appeals and argued in HW&D's brief: (1) whether the Commissioner of Food and Drugs was correct in his determination that Lutrexin was not exempt from both *administrative* and *judicial* enforcement of the effectiveness provisions of the Drug Amendments of 1962, by virtue of Section 107(c)(4) of those amendments; (2) whether the Commissioner was correct in his determination that Lutrexin was not exempt by virtue of Section 107(c)(2) of the 1962 Amendments, from *administrative* withdrawal of approval of its NDA under Section 505(e)(3) of the Act on the ground of lack of substantial evidence of effectiveness; (3) whether in any event the Commissioner was correct in determining that HW&D's product is a new drug subject to the provisions of Sec-

[5] That holding is before this Court for review in No. 394.

tion 505 of the Act as amended by the 1962 Amendments; and (4) whether the Commissioner was correct in denying HW&D an administrative hearing on these jurisdictional questions.

The Court of Appeals decided the first jurisdictional question adversely to HW&D, following its decision in *USV Pharmaceutical Corporation* v. *Richardson*, *supra*. It did not even mention the second and third questions. On May 23, 1972, the day before its decision in *Hynson* the Fourth Circuit had held that neither FDA nor the Court of Appeals on direct appeal under Section 505(h), 21 USC 355(h), had authority to determine the agency's jurisdiction. (*Bentex Pharmaceuticals, Inc.* v. *Richardson*, 463 F.2d 363, J.A. 258). Implicit in the Court's decision in *Hynson*, therefore, is a holding that FDA did not have the authority to consider these jurisdictional questions.

It is apparent that factual questions underlie the matter of whether Section 107(c)(2) and (4), or either of them, is applicable to Lutrexin, *viz.*, whether the drug was generally recognized as safe on the day before the effective date of the Drug Amendments of 1962 (October 9, 1962), within the meaning of Section 201(p), 21 USC 321(p), of the Act and was therefore not a new drug within the meaning of Clause (B) of Section 107(c)(4) of those amendments and not covered by an "effective" application within the meaning of Sections 107(c)(2) and 107(c)(4)(C) of the Amendments and whether the drug was being marketed in the United States on October 9, 1962, with the same labeling as is now in use, within the meaning of Section 107(c)(4). Underlying the third jurisdictional question above stated is the factual matter of whether Lutrexin is generally recognized *now* as both safe *and* effective within the meaning of Section 201(p) as amended in 1962. These are adjudicative facts determinative of the jurisdictional questions involved (See affidavits of

experts, J.A. 32 et seq.; medical literature, J.A. 87 et seq.).

Because of the *Bentex* ruling, evidence on the factual questions above-stated would not be considered by FDA or introduced at the hearing to which the Court of Appeals said HW&D was entitled since the hearing would be limited to the question of whether there is a lack of substantial evidence of the effectiveness of Lutrexin. Yet, if any one of the jurisdictional questions were decided in favor of HW&D, the question of whether HW&D is entitled to a hearing on the Commissioner's proposal to withdraw the license for its product under the new drug provisions of the Act would be moot.

SUMMARY OF ARGUMENT

1. In a proceeding to withdraw approval of a new drug application under Section 505(e)(3) of the Act, 21 U.S.C. 355(e)(3), the Food and Drug Administration (FDA) has the authority, subject to review by the Court of Appeals under Section 505(h), 21 U.S.C. 355(h), of the Act, to determine its own jurisdiction to conduct the proceedings, *e.g.*, whether a drug is a "new drug" within the meaning of Section 201(p), 21 U.S.C. 321(p).

A drug such as Lutrexin, which was once new and for which a new drug application had become effective, ceased to be "new" under the Act prior to its amendment in 1962, because it became generally recognized as *safe* by qualified experts (Section 201(p) as enacted in 1938) and is not "new" under the 1962 Amendments because it is generally recognized as both safe *and* effective.

FDA cannot properly conduct its business under the new drug section (Section 505) unless it has the authority to determine, initially, questions of jurisdiction. The decisions, including decisions of this court, clearly sup-

port our position that the agency has such authority in conducting proceedings such as the withdrawal-of-approval proceeding to which Lutrexin has been subjected.

2. The facts upon the basis of which FDA jurisdiction to conduct the withdrawal proceeding rests are adjudicative facts. Due process requires a hearing to establish the necessary facts to determine (a) whether Lutrexin is exempt from *administrative* withdrawal proceedings because of Section 107(c)(2) of the 1962 Amendments or from both *administrative* and *judicial* withdrawal proceedings by reason of Section 107(c)(4) of the Amendments, and (b) whether it is a new drug under the Act as amended in 1962.

There is a clear difference between the concept of "lack of substantial evidence of effectiveness" the basis for withdrawal of approval of an NDA under Section 505(e)(3) of the Act as amended in 1962, and the concept of general recognition of safety (Section 201(p) of the 1938 Act) and general recognition of safety *and* effectiveness (Section 201(p) as amended in 1962). The general recognition concept is solely a jurisdictional test which may be satisfied by adequate evidence of such recognition, but does not require, as the Government contends, the existence in the medical literature, of evidence of "substantial evidence of effectiveness" as used in Section 505(d) and (e) of the Act as amended in 1962. Section 201(p) contains no such requirement. The requirement appears only in Sections 505(d) and (e) and relates only to approval and withdrawal of approval, not general recognition of safety or effectiveness. The existence of studies showing substantial evidence of effectiveness therefore, although relevant, is not a *sine qua non* of a finding of effectiveness. Of course, the Act does not use the term "substantial evidence" in connection with proof of safety at all (as distinguished from proof of effectiveness). The cases do not support the position of the Government.

The facts relating to general recognition of safety as of October 9, 1962 (the day before the enactment date of the 1962 Amendments) must be ascertained in order to determine the application to Lutrexin of Section 107(c)(2) and (4) of the amendments. Whether the drug is now being marketed with the same labeling as was used on October 9, 1962, must be determined as a basis for ascertaining its status under Section 107(c)(4). Further, if Lutrexin is now generally recognized as both safe *and* effective Section 505 does not apply to it at all.

Our analysis of the medical data on Lutrexin, and the applicable cases, demonstrate, we believe, that FDA's decision of these underlying adjudicative facts without a hearing was wrong and a violation of due process.

3. Only those drugs whose NDAs were "effective" on October 9, 1962 are "deemed approved," by reason of Section 107(c)(2) of the Amendments; and only those NDAs "deemed approved" under that section are subject to withdrawal proceedings under Section 505(e) (except those *actually* approved under the Act as amended).

The NDA for Lutrexin became effective December 23, 1953. The drug had, however, become generally recognized as safe and had been used to a material extent and for a material time, prior to October 10, 1962, within the meaning of Section 201(p)(2) of the Act, as then in effect and was therefore no longer a "new drug." Since it was no longer a "new drug" on October 9, 1962, its NDA was on longer "effective" on that date and was therefore not "deemed approved."

An NDA for a drug which is no longer "new" is not "effective" in any legal sense.

As we show in the Argument, effective remedies under the Act other than administrative withdrawal of approval proceedings based on an alleged lack of substantial evidence of effectiveness, remain available to FDA.

4. It is our position that Lutrexin was not only not "deemed approved" under Section 107(c)(2) of the 1962 Amendments but is exempt from the effectiveness provisions of the Act by Section 107(c)(4) because, on October 9, 1962, it was commercially used or sold in the United States, was not then a "new drug," was not then "covered by an effective [new drug] application, and is marketed for the same conditions as it was on that date.

Section 107(c)(4) therefore protects the drug from *any* administrative or legal action based on alleged lack of effectiveness insofar as claims being made on October 9, 1962 are concerned. The legislative history reviewed in the Argument supports this position.

In the Argument we discuss the vagaries which inhere in the position of the Court of Appeals and the Government. Some of the confusion which has arisen in attempts to interpret the 1962 Amendments is clearly engendered by the imprecise language of the Amendments and their legislative history. Of the latter Senator Kefauver said: "Those in the future who attempt to study the legislative history of this measure as it passed through its various stages may be forgiven if they become somewhat confused." Clearly, however, the Government's position would deny any practical effect to the exempting provisions of Section 107(c)(2) and (4), contrary to the expressed intent of Congress.

ARGUMENT

I

THE COMMISSIONER OF FOOD AND DRUGS HAS THE AUTHORITY TO DETERMINE INITIALLY, SUBJECT TO JUDICIAL REVIEW, HIS OWN JURISDICTION UNDER THE NEW DRUG PROVISIONS OF THE ACT.

Basic Considerations and Legal Precedents

A. Introduction

The Fourth Circuit held in *Bentex* and *USV* that the Secretary (Commissioner of Food and Drugs) did not have authority in a new-drug withdrawal proceeding to ". . . adjudicate whether a drug meets the statutory criteria of a 'new drug' " and that the Court of Appeals reviewing an NDA-withdrawal order under Section 505(h) of the Act could not consider this jurisdictional question. Although the question was argued before the court in *Hynson*, the point was not mentioned by the Court in its opinion in the present case.[6] In *Ciba Corporation* v. *Richardson*, (J.A. 215) the Court of Appeals for the Third Circuit held:

> "Inherent in the grant of administrative competency to conduct and decide new drug proceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such a proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision" (J.A. 216).

HW&D's position is that the jurisdictional question of whether a drug is subject to the new drug provisions of the Act may be determined in at least the following ways:

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[6] Presumably the Court relied upon its holdings in *Bentex* and *USV*.

(1) Upon a challenge to his jurisdiction in a proceeding to withdraw approval of an NDA under Section 505 (e) of the Act, the Commissioner may, based upon evidence adduced at an adjudicative hearing, determine the new drug status of the product involved, subject to judicial review.

(2) The jurisdictional question may be raised in an enforcement proceeding based on Section 505 of the Act; and

(3) A drug manufacturer may by a declaratory judgment action have the jurisdictional question resolved by a United States District Court.

B. Background

Prior to the proceedings involving the withdrawal of approval of the NDA for HW&D's product, the Commissioner had not adopted the position that the agency would entertain challenges to its jurisdiction over drugs as "new drugs" in NDA-withdrawal proceedings.

After receipt of the Commissioner's notice of an opportunity for a hearing on his proposal to withdraw approval of the NDA for Lutrexin (J.A. 12), HW&D filed with the Commissioner a letter electing to accept the opportunity for a hearing, but reserved the right to contest the jurisdiction of the Commissioner over Lutrexin as a "new drug" (J.A. 14). Thereafter, HW&D filed its complaint in the Federal District Court in Baltimore (*Hynson, Westcott & Dunning, Inc.* v. *Finch*, No. 21112) seeking a declaratory judgment that Lutrexin is not subject to regulation by the Commissioner as a "new drug."[7] At the hearing on the Government's motion to dismiss, counsel for the Commissioner agreed to the Court's suggestion that the agency consider the jurisdictional points in the administrative proceedings.

[7] See J.A. 15 for a summary of the allegations of the complaint.

The result of the District Court's Order was that for the first time the Commissioner had to make a determination on the record before it of its jurisdiction, *vel non*, over a drug product.

C. Judicial Precedents

The Fourth Circuit in *Bentex* and *USV* cited no decisions to support the proposition that the Commissioner does not have the authority to initially determine his jurisdiction over a drug as a "new drug" or to determine the coverage of the 1962 Amendments in particular cases. Neither did the third Circuit in *Ciba* present any authorities for its holding to the contrary.

There is, however, ample support in decisions by this court and lower federal courts for the *Ciba* holding that federal agencies have the inherent authority to determine initially their own jurisdiction, subject to appellate review.

As early as 1904, this court, speaking through Mr. Justice Holmes, held that a customs inspector, whose jurisdiction to deny admission of an alien was challenged, must determine his jurisdiction and if he decides it exists, go forward with administrative proceedings including review of his decision by Secretary of Commerce.[8] This court has also upheld the authority of the Bituminous Coal Commission and the Interstate Commerce Commission to decide initially, subject to appellate review, the question of the coverage of their respective statutes.[9] In the *Yonkers* case the Commission was presented with an application by a railroad company for a certificate allowing the company to abandon a portion

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[8] *United States* v. *Sing Tuck*, 194 U.S. 161 (1904).

[9] *Sunshine Anthracite Coal Co.* v. *Adkins*, 310 U.S. 381, 399-400 (1940); *City of Yonkers* v. *United States*, 320 U.S. 685, 689-692 (1944).

of an electric branch line. Under Section 1(22) of the Interstate Commerce Act, the Commission's authority to issue such certificates does not extend to electric railways ". . . which are not operated as a part or parts of a general steam railroad system of transportation." The question of the Commission's jurisdiction under Section 1(22) was not raised during the administrative hearings but was raised in petitions for reconsideration of the agency's order. These petitions were denied by the Commission without opinion, with the result that there were no agency findings concerning the Commission's jurisdiction over the electric branch line involved. This court held that the Commission should have determined the jurisdictional question upon appropriate findings based upon evidence of record. Mr. Justice Douglas put it this way:

> ". . . the determination of what is included within the exemption of § 1(22) involves a 'mixed question of fact and law.' Congress has not left that question exclusively to administrative determination; it has given the courts the final say. . . . But we deem it essential in cases involving a review of orders of the Commission for the courts to decline to make that determination without the basic jurisdictional findings first having been made by the Commission" (320 U.S. at 689).

This court has also upheld the authority of the Wage and Hour Administrator, in the first instance, to determine questions of coverage under the Fair Labor Standards Act, *Oklahoma Press Pub. Co.* v. *Walling*, 327 U.S. 186, 214 (1946), and the authority of the Secretary of Labor to determine initially the coverage of the Walsh-Healy Public Contracts Act, *Endicott Johnson Corporation* v. *Perkins*, 317 U.S. 501, 507-509 (1943). Most recently this court held that the Federal Power Commission had the authority to initially decide its jurisdiction to certificate a particular pipeline delivery when a certi-

fication proceeding to determine that question was pending before the Commission. *Federal Power Commission* v. *Louisiana Power & Light Co.*, 406 U.S. 621 (1972). Of particular importance to the case at bar is the following statement of the Court per Mr. Justice Brennan:

> "The need to protect the primary authority of an agency to determine its own jurisdiction is obviously greatest when the precise issue brought before a court is in the process of litigation through procedures originating in the [agency]. While the [agency's] decision is not the last word, it must assuredly be the first" (406 U.S. at 647).

The lower federal courts have consistently upheld the propriety of initial determination by federal agencies, of their jurisdiction, followed by judicial review. *Federal Power Commission* v. *Arizona Edison Co.*, 194 F.2d 679, 683-684 (9th Cir. 1952); *J. M. Huber Corporation* v. *Denman*, 367 F.2d 104, 111-112 (5th Cir. 1966), cert. denied, 352 U.S. 971; *Brooklyn Eastern District Terminal* v. *United States*, 302 F.Supp. 1095, 1107 (D. N.Y. 1969); *Fontaine* v. *Securities and Exchange Commission*, 259 F.Supp. 880, 884 (D. Puerto Rico 1966); *Southern Pacific Company* v. *National Mediation Board*, 223 F.Supp. 951, 952 (D. D.C. 1963).

In *Arizona Edison, supra*, the court held that the Federal Power Commission had authority to determine the coverage of the Federal Power Act, i.e., to classify a company as a "public utility" subject to regulation by the agency. The court said:

> ". . . the Company's contentions appear to be that a judicial determination of 'public utility' status must be made before the Commission can act. A review of the Federal Power Act demonstrates that its administration is unmistakably conferred upon the Commission and broad powers of rulemaking, prosecuting and adjudicating are given it. . . We think

> that the orderly procedure inherent in the statutory scheme contemplates that the Commission in the exercise of its broad regulatory powers may determine coverage of the Act. . ." (194 F.2d at 683).

In *Southern Pacific, supra,* Judge Holtzoff described the procedure that HW&D considers the proper method for resolution of jurisdictional disputes arising in NDA-withdrawal proceedings before the Food and Drug Administration. The action was one to enjoin the National Mediation Board from taking jurisdiction of a dispute. The court exercised its discretionary power to send the matter back to the agency for initial determination of the questions involved, and denied the motion for injunction, but with leave to renew if the Board failed or declined to make a ruling on the question of its own jurisdiction.[10] Judge Holtzoff stated in part:

> "The Court assumes, of course, that the National Mediation Board will hear and determine the objections to its jurisdiction before proceeding with hearing and determining the merits of the dispute and that if it finds that it has no jurisdiction it will stop at that point. If, however, it finds that it does have the jurisdiction, it would have the authority to proceed with a hearing and reach a decision" (223 F.Supp. at 952).

Based upon the foregoing precedent, it is submitted that the Commissioner of Food and Drugs could properly entertain a challenge to its jurisdiction in an NDA-withdrawal proceeding under Section 505(e), provided that appropriate procedural safeguards, including the right to an adjudicatory hearing, are employed. These matters are discussed in Point II, *infra.*

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[10] The position taken by the court is thus similar to that taken by the District Court in *Bentex,* with which we concur, *viz.,* that the District Courts and the Commissioner have concurrent jurisdiction to determine the coverage of the new drug provisions of the Act.

II

A MANUFACTURER WHOSE DRUG IS THE SUBJECT OF A PROCEEDING TO WITHDRAW APPROVAL OF A NEW DRUG APPLICATION IS ENTITLED TO AN ADMINISTRATIVE HEARING ON THE QUESTION OF WHETHER THE COMMISSIONER HAS JURISDICTION TO CONDUCT SUCH A PROCEEDING.

A. The Necessity Of Distinguishing Between Proof Of General Recognition Of Safety Or Effectiveness And Proof Of Lack Of Substantial Evidence Of Effectiveness.

(1) *Introduction*

Although some of the terms used in the new-drug provisions of the Act are not readily understood, the structure of those provisions is simple. The pertinent part of the definition of the term "new drug" in Section 201(p) is whether a drug is ". . . generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective . . ." for its intended uses.

A drug which *is* a "new drug" under Section 201(p) is subject to the requirements of the new drug provisions of Section 505. Such a new drug cannot be marketed without an approved NDA supported by "substantial evidence" of effectiveness as defined in Section 505(d) of the Act. Approval of the NDA for a new drug may also be withdrawn by the Commissioner if he finds that, for various reasons detailed in Section 505(e), there is "a lack of substantial evidence" of the effectiveness of the new drug as the quoted term is defined in Section 505(d).

The term "substantial evidence," as used in Section 505(d) and Section 505(e), means:

> ". . . evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof" (Section 505(d)).

The Commissioner has promulgated regulations specifying the principles which provide the basis for ". . . the determination whether there is 'substantial evidence' to support the claims of effectiveness for 'new drugs'" (21 C.F.R. 130.12(a)(5); J.A. 487), including the types of controls which must be utilized in studies of the effectiveness of new drugs.[11]

Under the terms of the statute it is clear that the "lack of substantial evidence" test prescribed in Section 505(d) is applicable only to proof of the actual effectiveness of drugs which fall within the definition of "new drug" prescribed in Section 201(p). A determination that a drug is not generally recognized by qualified experts as safe and effective for its intended uses, and is therefore a "new drug" under Section 201(p), is a condition precedent to the application to the drug of the new drug provisions in Section 505, including application of the "lack of substantial evidence" test in Section 505(d).

The Commissioner, however, in the order withdrawing approval of the NDA for HW&D's Lutrexin (J.A. 72) elaborated a new theory which would require a manufacturer seeking to prove its drug not to be a new drug under Section 201(p), to present proof of actual effectiveness of the drug under the "lack of substantial evi-

[11] The question of the validity of these regulations arises in No. 72-394.

dence" test prescribed in the new drug provisions of the Act. Under this theory, evidence of the type required for the marketing of new drugs under Section 505(d), including adequate and well-controlled studies, must be shown to exist as a condition precedent to the application of the test of whether a product is a new drug within the meaning of Section 201(p) of the Act.

Thus, the order withdrawing approval of the Lutrexin NDA denied HW&D a hearing on the question of whether the drug is a new drug on the following grounds:

> "No adequate and well-controlled clinical investigations published in the medical literature have been identified.[12] Therefore, there is no data base upon which experts can fairly and responsibly conclude that the safety and effectiveness of . . . . [Lutrexin] has been proven and is so well established that . . . [Lutrexin] can be generally recognized among such experts as safe and effective for . . . [its] intended uses" (J.A. 72 at 74).

We shall show below that there is no basis for this conclusion.

(2) *Legislative History*

The Government in its brief in the court below, and in its memorandum in response to HW&D's cross-petition for certiorari (pp. 6-7), argued that the legislative history of the 1962 Amendments supports its contention that "substantial evidence of effectiveness" in the form of adequate and well-controlled investigations (Section 505(d) as amended in 1962) must be identified in the medical literature in order to provide a basis for a conclusion by qualified experts that a drug is generally

[12] The "substantial evidence" test prescribed in Section 505(d) for new drugs.

recognized as safe and effective. The test for general recognition of safety and effectiveness, the government maintained, can be derived from an examination of the medical testimony presented before the Senate Subcommittee on Anti-trust and Monopoly concerning the basis for the "substantial evidence" test.[13]

The Government's reliance on this legislative history is misplaced. It is unquestionably clear that the medical testimony cited in the brief below went directly to the type of evidence needed to show the effectiveness of new drugs, under the new-drug licensing provisions of the Act (Section 505). It had nothing at all to do with the question of the evidence required to show whether a drug *is* a "new drug" or not, that is, the type of evidence required to prove general recognition of safety and effectiveness.

Although it could have done so, Congress did not require qualified experts to base their expert conclusions of general recognition on the existence of adequate and well-controlled studies in the medical literature. It could not have done so on the basis of the medical testimony cited in the Government's brief below, since that testimony had nothing to do with the type of evidence required to support an expert's conclusion that a drug is generally recognized as safe and effective. Congress was concerned with the effectiveness of "new drugs", drugs which experts did not recognize to be safe and effective. This concern led to the inclusion of "general recognition of effectiveness" in the definition of new drug, but not to a specification of the evidence upon which a qualified expert must base his conclusion as to general recognition. Congress prudently left to the qualified expert the decision of the type of evidence which would cause him to

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[13] See, *e.g.*, Hearing before the Subcommittee on Anti-trust and Monopoly, Senate Judiciary Committee, 86th Cong., 2d Sess., p. 243.

conclude that a product was generally recognized as safe and effective.

(3) *Judicial Precedents*

FDA is asking this court, in effect, to judicially amend Section 201(p)(1) by adding to the definition of "new drug" in that section the definition of the term "substantial evidence" set forth in the provisions of the Act regulating new drugs (Section 505(d)). Proof of substantial evidence of effectiveness based upon adequate and well-controlled studies would involve a showing of the actual effectiveness of a drug. No cases have been cited by the Government which accept this theory. Indeed, to adopt the theory would be to overrule a legal principle firmly established by the courts. As stated by Judge Thomsen of the Maryland federal district court in a case involving the new drug status of a product:

> "In such a case as this, the court does not decide whether the drug is safe and effective; the court lacks the necessary expertise to make that decision. * * * The question which this court must decide in this case . . . is whether the Government has shown by a preponderance of the evidence [14] that the 'drug' is not generally recognized by qualified experts as safe and effective for use. . . .' " *United States* v. *Articles of Drug Labeled "Quick-O-ver"*, 274 F. Supp. 443, 445-446 (1967).

This distinction was also made in *Amp. Incorporated* v. *Gardner*, 389 F.2d 825, 831 (2d Cir. 1968), cert. denied, sub nom *Amp. Inc.* v. *Cohen*, 393 U.S. 825, rehearing denied 395 U.S. 917: " . . . the safety of the products is not what is at issue here. The question is whether there is general recognition among qualified experts of the products' safety and effectiveness. . ."; in *United States* v. *An Article of Drug* * * * *Excedrin, P.M.*

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[14] FDA has offered no evidence in the case at bar.

CCH Food, Drug & Cosmetic Law Reporter, ¶ 40,486 at page 41,226 (D. N.Y., March 5, 1971, No. 70-C-77): "the issue is general recognition, and not whether the drug is in fact safe and effective"; in *United States* v. *Article Consisting of 36 Boxes, Etc.*, 284 F.Supp. 107 at 112 (D. Del. 1968): ". . . the question is not whether in point of fact Line Away is unsafe or ineffective. It is whether qualified experts generally recognize Line Away to be unsafe or ineffective"; and in *United States* v. *Article of Drug, Etc.*, 294 F.Supp. 1307 (D. Ga. 1968), aff'd, 415 F.2d 390 (5th Cir. 1969), where the court said:

> "The court is not required to find that the drug Furestrol is actually unsafe or ineffective for its intended uses. It must be proven . . . that Furestrol was not generally recognized by qualified experts as being both safe and effective . . . (294 F.Supp. at 1310). * * *
>
> The court does not hold that Furestrol is unsafe or ineffective; however, this court does rule that Furestrol . . . is a new drug within the meaning of 21 USC § 321(p)(1), since it is not generally recognized as safe and effective . . ." (294 F.Supp at 1311).

The requirement as a basis for the determination of general recognition of safety and effectiveness of a showing of substantial evidence of effectiveness, cannot, therefore, be justified under the Act. The decisions cited above unanimously hold that actual safety is not the proper test of the status of a drug under § 201(p)(1)—the proper test is general recognition by qualified experts.

This is not to say that the existence of adequate and well-controlled studies in the medical literature is irrelevant in determining whether a drug is generally recognized as effective. Existence of controlled studies as well as other studies in the medical literature has been held relevant to such a determination. See, *e.g.*, *United States*

v. *Article of Drug, Etc.*, 294 F.Supp. 1307 (D. Ga 1968), aff'd, 415 F.2d 390 (5th Cir. 1969). Existence of controlled studies is not, however, the sole criterion which may be utilized by qualified experts to determine the general recognition question. Congress did not specify in Section 201(p) the evidence upon which experts could decide the question. The following criteria have been considered relevant in past cases and were used by HW&D's affiants in the instant case (J.A. 32 et seq.): clinical experience in the use of the drug in treatment of patients, expertise in the disease for which the drug is indicated, knowledge of the opinions of other physician-experts concerning the safety and effectiveness of the drug, and existence in the medical literature of studies, controlled or otherwise, demonstrating the safety and effectiveness of the drug. See *United States* v. *Article of Drug, Etc.*, *supra*, at 1308-1309. In a given case the existence of well-controlled studies may indicate that the drug involved has been shown to be actually effective but the drug may nevertheless not be recognized generally by qualified experts to be effective for its intended uses. On the other hand, a drug may have enjoyed such widespread use and therapeutic success that qualified experts could conclude that it is generally recognized as safe and effective, even if no studies of any kind existed in the medical literature.

In any event the attempt to incorporate the "substantial evidence" definition into Section 201(p)(1)' is doomed to failure because of one inescapable fact: the concept of substantial evidence in Section 505(d) relates only to the effectiveness of a drug; it has no relation to the safety of a drug. Section 201(p)(1), on the other hand defines a "new drug" in terms of general recognition of *safety* and effectiveness. There is no statutory provision concerning substantial evidence of safety. The Government's position would therefore lead to the incongruous result that substantial evidence of effectiveness would be required as a condition of a determination of general

recognition of effectiveness but no such evidence would be required for a determination of general recognition of safety.

B. The Requirement Of A Hearing To Determine The New Drug Status Of Lutrexin

(1) *Introduction*

In *Hynson, Wescott & Dunning, Incorporated* v. *Finch*, (C.A. No. 21112, D. Md. 1970),[15] HW&D was prepared to offer factual proof at a trial, and is prepared to do so in a hearing before FDA, to support its contentions that Lutrexin was generally recognized as safe prior to October 10, 1962, and that the product is now generally recognized as both safe and effective. This proof was and is available in the form of expert testimony by physicians who have studied and used Lutrexin extensively, as well as in the form of literature (See J.A. 32 et seq.; 87 et. seq.). The proper and legally required method of presenting such proof should have been at an adjudicative or trial-type hearing where the expert testimony could have been tested by cross-examination, as well as by presentation of any evidence available to the government in rebuttal.

Unfortunately, however, this court does not have before it for review an order based upon any evidence adduced at a trial or hearing. The order is based upon a rejection by FDA of the evidence proffered by HW&D, in its renewed request for a hearing, dated October 16, 1970. The affidavits, studies, and other data, which will be briefly summarized below, were presented to the Agency as a showing that there exists solid evidence to support HW&D's claims of general recognition of safety prior to October 10, 1962 and of general recognition of safety and effectiveness today—evidence which clearly raises questions

[15] A summary of the Complaint in that case appears at J.A. 15.

of fact which should have been resolved in an adjudicative administrative hearing.

As a result, the order before the Court of Appeals and this court cannot be accorded the usual deference due to a determination by an expert administrative agency based upon substantial evidence[16] adduced at a hearing. *Citizens to Preserve Overton Park, Inc.* v. *Volpe*, 401 U.S. 402, 414 (1971). To defer to FDA's expertise in this case, where no hearing was held and where FDA offered no evidence to support its order, would fulfill the fears expressed by this court that "Administrative expertise would be on its way to becoming 'a monster which rules with no practical limits on its discretion'." *Baltimore & Ohio R. Co.* v. *Aberdeen & R.R. Co.*, 393 U.S. 87, 92 (1968).

(2) *Brief Summary Of Medical Data Contained In Appendix*

The safety of Lutrexin has not been questioned. The affidavits of six medical experts (J.A. 32 et seq.), as well as the medical studies (J.A. 87 et seq.), submitted to the Commissioner in HW&D's request for a hearing on the jurisdictional points demonstrate conclusively that the drug is not only safe but was generally so recognized for at least ten years before the execution of the affidavits. The affidavits and studies also demonstrate that the drug is now generally recognized as both safe and effective. All told the affiants have treated over two thousand patients with Lutrexin, in dosages of up to 36,000 units in a twenty-four hour period with no side effects to mother or child. Reports on Lutrexin have been made by seven medical experts in obstetrics and gynecology, and no side

[16] We are here, of course, using this term in the normal administrative law sense, rather than as defined in Section 505(d) of the Act.

effects were reported. A few quotations from the reports and from a statement of a member of the NAS-NRC panel which reviewed Lutrexin indicate the conclusions of the experts as to the effectiveness of Lutrexin:

(a) Dr. Majewski's first two studies report on use of Lutrexin in 79 patients threatening to give birth prematurely (J.A. 92, 99). The contractions were halted in 68.4% of the patients, giving ". . . 54 babies a longer time to gain weight and to develop within the uterus, thus increasing their chances of survival and lessening the possibility of their suffering from the congenital diseases so often associated with prematurity" (J.A. 104);

(b) Dr. Rezek's 1953 paper presents 54 cases of Lutrexin treatment of premature labor. Labor was halted in 74% of the patients for at least 28 days ". . . enabl . . . [ing] many fetuses to survive that otherwise would have died because of prematurity" (J.A. 118 at 120).

(c) Dr. Gratton's study involved 219 women with a history of premature deliveries: "After using Lutrexin in a small number of problem cases and noting the apparent beneficial effect, it was decided to utilize this drug in all cases of premature labor, threatened abortion and habitual abortion. Experience gained over approximately ten years has amply shown the value of Lutrexin in the treatment of such patients. Before using this drug, only 46% live births were obtained in 446 pregnancies, whereas with the use of Lutrexin, 79.8% live births were achieved. The differences noted with, and without, Lutrexin were highly significant (P=.001) in the entire study herein reported. Significant differences (P=.001 to .05) were observed in patients with one to five previous pregnancies" (J.A. 87 at 88-89).

(d) Dr. Willard M. Allen, one of only two physicians expert in obstetrics and gynecology on the panel of the National Academy of Sciences-National Research Council which reviewed the effectiveness of Lutrexin (J.A. 5), made in a notarized letter to HW&D the following statements concerning the drug:

> "Lutrexin contains a biologically active component (as yet unidentified structurally) which has a relaxing effect on the uterus of the laboratory animals and women. . . .
>
> "The clinical evidence which you have submitted, and which I have read carefully, does indicate that Lutrexin is beneficial in the three conditions for which it is recommended. The evidence also indicates the Lutrexin is not harmful or dangerous either to the patient or to the fetus. . . . (J.A. 47-48).

(3) *Judicial Precedents*

This court has stressed the importance of the requirement that administrative decisions be based on ". . . substantial evidence and reasoned findings—which alone make effective judicial review possible. . . ." *Baltimore & Ohio R. Co.* v. *Aberdeen & R.R. Co.*, 393 U.S. 87, 92 (1968). The jurisdictional question of whether a product is generally recognized as safe and effective for its intended uses and is, therefore, a new drug, involves a mixed question of fact and law. *City of Yonkers* v. *United States*, 320 U.S. 685, 689. The affidavits of medical experts and medical studies submitted by HW&D in support of its request for a hearing on the general recognition question were certainly adequate to raise genuine and substantial issues of fact requiring resolution at an adjudicatory hearing. The Commissioner offered no affidavits or medical data in support of his denial of a hearing.

Under these circumstances the Commissioner's order violated due process of law. *Goldberg* v. *Kelly*, 397 U.S. 254, 269-270; *ICC* v. *Louisville & N.R. Co.*, 227 U.S. 88, 93-94 (1913). As stated by Mr. Justice Brennan in *Kelly*, *supra*, "In almost every setting where important decisions turn on questions of fact, due process requires an opportunity to confront and cross-examine witnesses" (397 U.S. at 269).

In any event, even had the Comissioner presented affidavits in support of his conclusion that Lutrexin was not a new drug, an adjudicative hearing would have been required. The situation would be analogous to that which arises on cross-motion for summary judgment supported by affidavits in District Court cases on the question of whether a drug is generally recognized as safe and effective. Although some doubt existed on the point in earlier decisions,[17] the law seems settled that when genuine differences of opinion exist among experts as to whether a drug is generally recognized as safe and effective, these differences present factual issues requiring a trial. *United States* v. *Article Consisting of 36 Boxes, Etc.*, 284 F.Supp. 107, 113 (D. Del. 1968), aff'd. 415 F.2d 369 (3rd Cir. 1969); *United States* v. *7 Cartons, More or Less, Etc.*, 293 F.Supp. 660, 662-663 (D. Ill. 1968);[18] *Lemmon Pharmacal Co.* v. *Richardson*, 319 F.Supp. 375, 378 (D. Pa. 1970); Cf. *United States* v. *Article of Drug* *** *"Mykocert,"* 345 F.Supp. 571, 574-575 (D. Ill. 1972).

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[17] See, *e.g.*, *Merritt Corporation* v. *Folsom*, 165 F.Supp. 418 (D. D.C. 1958); cf. *AMP, Inc.* v. *Gardner*, 389 F.2d 825, 831 (2d Cir. 1968), cert. denied, 393 U.S. 825, and *United States* v. *1,048,000 Capsules, More or Less, etc.*, 347 F.Supp. 768, 770-771 (D. Tex. 1972).

[18] The case was appealed, 424 F.2d 1364 (7th Cir. 1970). The decision of the District Court on the new drug question was not adopted by the Seventh Circuit since the case could be disposed of on other grounds.

The Commissioner in his order withdrawing approval of the Lutrexin NDA, denied HW&D a hearing on the ground that the data submitted by HW&D did not show existence of adequate and well-controlled studies in the medical literature.[19] The Commissioner attempted to support the denial with a factual analysis of the studies submitted by HW&D in its request for a hearing (J.A. 72, 74). Even if it be assumed that "adequate and well-controlled studies" are necessary for a determination that a drug is generally recognized as effective, the Commissioner's analysis itself demonstrates the existence of substantial issues of fact which cannot appropriately be resolved by a reviewing court without the benefit of a record based upon expert evidence adduced at a hearing before FDA.

The Commissioner said, for example:

(1) With respect to Dr. Majewski's first two studies: ". . . Six patients received the drug for less than three hours, which the authors without explanation considered too short a time for a true test of effectiveness" (J.A. 72, 75).

(2) With respect to Dr. Majewski's third study: "Substantiating documentation to establish an historical control and percentage of patients with medical or surgical complications of pregnancy is not provided. . . . The data in Table I does not admit of statistical evaluation by the chi square test since the test is based on the assumption that each number in the columns of Table I is the sum of independent yes or no responses. . . ." (J.A. 72, 75).

(3) With respect to Dr. Rezek's first study: "Concomitant medication is not excluded * * * No explanations of the methods of observation, the

[19] The lack of legal basis for this approach is discussed in Point II A.

recording of results, and steps taken to minimize patient and investigator bias are provided" (J.A. 76).

(4) With respect to Dr. Gratton's study: The pairings of live births percentages in Table II cannot be compared since the number of previous pregnancies differs between the pair percentages and there is no data on possible factors of previous abortions and premature labor." (J.A. 76).

These purport to be findings of fact which obviously are considered material by FDA. The findings raise issues of fact as to the nature of the studies which can be resolved only by expert testimony at a hearing. As stated by the Court below in connection with denial of a hearing by FDA on the proposal to withdraw the Lutrexin NDA:

> "Assuming that all the objections by the Commissioner . . . [to the HW&D studies] may have some validity, they do not justify a final conclusion . . . that it 'clearly appears' that there is no genuine issue of fact . . .; at most they merely create a genuine question of fact to be resolved at a hearing upon proper evidence" (J.A. 173, 180).

Without the benefit of a full record based upon expert testimony as to the medical and scientific validity of FDA's objections and the affidavits and studies themselves, a reviewing court is not in a position to decide the complex questions involved. Criticisms such as "the data . . . does not admit of statistical evaluation by the chi-square test . . ." raise questions of fact which can be resolved only by experts.[20]

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[20] See *United States* v. *1,048,000 Capsules, More or Less, Etc.*, 347 F.Supp. 768, 773-776 (D. Tex. 1972) for examples of the type of expert testimony needed to enable a court to determine both the questions of general recognition and of adequate and well-controlled studies. The court stated in that case, in connection with its

We have shown, *supra*, that the affidavits and medical literature submitted to FDA pose factual questions whose resolution is a prerequisite to a determination of whether FDA has jurisdiction under Sections 201(p) and 505 of the Act, *e.g.*, whether Lutrexin was generally recognized as safe on the day before the enactment date of the 1962 amendments (i.e. on October 9, 1962) and was therefore not a "new drug" under Section 201(p) as then in effect and whether Lutrexin is now generally recognized as both safe *and* effective and is therefore not a "new drug" under Section 201(p) as amended by the 1962 Amendments.

The situation is clearly distinguishable, therefore, from that in *Dyestuffs & Chemicals, Inc.* v. *Flemming*, 271 F.2d 281 (8th Cir. 1959), where petitioner was held not entitled to a hearing before the Secretary (FDA) upon a matter with respect to which the Supreme Court had held (*Flemming* v. *Florida Citrus Exchange*, 358 U.S. 153 (1958)) that he had no authority to act. In *Dyestuffs* the Court said—

> "Where the objections stated and the issues raised thereby are, even if true, legally insufficient, their effect is a nullity. . . ." 271 F.2d at 286.

Obviously that is not the situation here since the facts cross-petitioner has already presented indicate that FDA does not have the jurisdiction which it claims over Lutrexin.

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discussion of testimony on the question of a product's "new drug" status:

> "It is a substantive area in which the layman including this court can readily lose his way in a morass of technical terms, which, once comprehended, serve to bridge and lead to an understanding of the professed uses of Afrodex in the pharmacological, medical and psychiatric fields. Whatever the extent of this litigation, this articulation of expert opinion should assist in graphically underscoring the reasons why this court is persuaded to hold as it does today" (347 F.Supp. at 773).

Nor is this case like *Sun Oil Co.* v. *Federal Power Commission*, 256 F.2d 233 (5th Cir. 1958), cert. denied, 358 U.S. 872 where no fact question was involved and the court found that "The only benefit that would have inured to Sun by notice and hearing would have been the privilege of making a legal argument before the Commission", which neither due process nor the statute required (256 F.2d at 240-241); or *United States* v. *Storer Broadcasting Company*, 351 U.S. 192 (1956), where petitioner concededly "owned" more television stations than a rule of the Federal Communications Commission permitted; or *Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33 (1964), where a petition was patently not in proper form because of certain price-changing provisions in the contracts filed with the petition, which were not permissible under a rule of the Commission.

The "Rules of Evidence for United States Courts and Magistrates" (Federal Rules of Evidence) were adopted by the Supreme Court November 20, 1972, to take effect July 1, 1973. (468 F.2d—No. 2, Advance Sheets, January 1, 1973, p. 1). In its notes on Rule 201, entitled "Judicial Notice of Adjudicative Facts," the Advisory Committee stated that its note "draws extensively" upon the writings of Professor Davis (Id. at 18) and quotes from his definition of adjudicative facts in his Administrative Law Treatise, Section 15.03, p. 353, as "those to which the law is applied in the process of adjudication. . . . They relate to the parties, their activities, their properties, their business" Id. at 20. Adjudicative facts are distinguished from legislative facts which are those upon the basis of which the applicable law and policy have been previously established. Administrative Law Treatise at p. 353.

We think it clear that the facts involved in a determination of whether Lutrexin is within the coverage of the Act and the 1962 Amendments are adjudicative

facts. They relate to the activities and business of Hynson, Westcott & Dunning in its marketing of Lutrexin under rules previously established by Congress. Thus, the questions of general recognition of safety or effectiveness of the drug, and of what labeling it bore on the day preceding the enactment date of the 1962 Amendments can relate only to Lutrexin. The answers to those questions are not pertinent to any other drugs or their status under the Act.

The law requires a trial-type hearing to determine those facts. Davis, Administrative Law Treatise, 1970 Supplement, Sections 7.01, 7.04.[21] Such a hearing may be held as a part of or ancillary to the trial-type hearing which the Fourth Circuit held was required in a proceeding to determine whether there is a lack of substantial evidence of the effectiveness of Lutrexin, which also involves adjudicative facts. (The necessity for a hearing on the question of whether there is a lack of substantial evidence of the effectiveness of Lutrexin will be discussed in our reply brief in *Richardson* v. *Hynson, Westcott & Dunning*, No. 394).

It is apparent from the leading case of *Myers* v. *Bethlehem Shipbuilding Corporation*, 303 U.S. 41 (1938) that an agency, in determining the question of its own jurisdiction, must do so on the basis of evidence adduced at a hearing. There is nothing in the Federal Food, Drug and Cosmetic Act to justify a different conclusion on this point than that reached in *Myers*.

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[21] It is our view that such a hearing should have been afforded by the District Court in *Hynson, Westcott & Dunning* v. *Finch* (CA No. 21112, D. Md., September 11, 1970, J.A. 23), but that it must be afforded administratively in a withdrawal proceeding under Section 505(e)(3) if it has not been decided in the Courts and is made an issue by a party.

If the adjudicative facts on the question of coverage are found to be contrary to the present position of the agency, either by the Agency or the Court of Appeals, the withdrawal proceeding will become irrelevant and moot.

III

LUTREXIN WAS NOT "DEEMED APPROVED" UNDER SECTION 107(c)(2) OF THE DRUG AMENDMENTS OF 1962 AND HENCE WAS NOT SUBJECT TO ADMINISTRATIVE WITHDRAWAL PROCEEDINGS UNDER SECTION 505(e)(3) OF THE ACT.

Section 107(c)(2) of the Drug Amendments of 1962 provides that—

> "(c)(2) An application filed pursuant to Section 505(b) of the basic Act which was 'effective' within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application 'approved' by the Secretary within the meaning of the basic Act as amended by this Act."

In 1962 Section 505 of the Act was amended to read in terms of "approval" of an application, replacing the language of the Act as enacted in 1938, which referred only to applications becoming "effective." Thus, Section 505(e) authorizes the Secretary (Commissioner) to "withdraw approval" of an application "(3) . . . if there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have . . .".

Consequently, only applications "deemed approved" under Section 107(c)(2), or actually approved under the Act as amended in 1962, can be subject to withdrawal of approval proceedings.

The day immediately preceding the enactment date of the 1962 Amendments was October 9, 1962. An appli-

cation which was "effective" on that date is "deemed approved" under Section 107(c)(2) and therefore was subject to administrative withdrawal proceedings under Section 505(e)(3) of the Act on the ground of lack of substantial evidence of effectiveness. But such withdrawal proceedings, based on old claims effectiveness, could not be brought for two years after the enactment dates of the 1962 amendments because of Section 107(c)(3)(B).

FDA contended below that Lutrexin was "deemed approved" and "approval" was, therefore, subject to withdrawal under Section 505(e)(3) two years after the enactment date. This theory was cited as legal support for its withdrawal order (J.A. 72, 74).

Concededly, however, the NDA for Lutrexin was never *actually* approved by FDA since, in 1953, when it was filed and reviewed by FDA, there was no provision for approval of NDA's. They simply became "effective" after a stated statutory period unless they were denied.

It is our position, which is supported by the affidavits of experts reproduced in the Joint Appendix (p. 32 et seq.), that Lutrexin had, as of the day before the enactment date of the 1962 Amendments, become generally recognized as safe and had been used to a material extent and for a material time, within the meaning of Section 201(p)(2) of the Act as then in effect, and was therefore no longer a new drug. Since it was no longer a new drug on October 9, 1962, the NDA for Lutrexin was no longer "effective" on that date and was therefore not "deemed approved" under Section 107(c)(2) of the 1962 Amendments.

A "new drug" could not be marketed under the 1938 Act without an "effective" NDA. It is clear that an "effective" application is one which authorized the marketing of the "new drug" which is the subject of the

application. If the drug is no longer "new" within the meaning of the Act (Section 201(p), 21 USC 321(p)), it is apparent that the application has no legal effect at all. Thus, if FDA purported to approve an application for a drug which was not a "new drug" within the meaning of Section 201(p), the application could not become legally "effective". It is the same where a drug was no longer "new" on October 9, 1962, and therefore no application was "effective" with respect to it on that date.

Otherwise stated, an NDA of a drug which is no longer new has no viability—is of no legal effect. Neither in logic nor law can there be an "effective" *new drug* application for a drug which is not a *new drug*. Certainly this approach reflects the ordinary meaning of the term "effective" and, in the absence of an indication in the statute or its legislative history the ordinary meaning should, we submit, be accepted.

It should be emphasized that our conclusion that Lutrexin was not "deemed approved" excuses it from administrative withdrawal of approval of its NDA under Section 505(e)(3), but not from judicial proceedings under Section 505, such as seizure, criminal prosecution and actions for injunctions based on allegations of a lack of general recognition of effectiveness.[22] It is exempt from these judicial proceedings only if it meets the three conditions of Section 107(c)(4) hereinafter considered (Point III) and then only with respect to old claims of effectiveness being made on October 9, 1962.

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[22] Section 505(a), 21 U.S.C. 355(a): "No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug." Section 301, 21 U.S.C. 321: "The following Acts and the causing thereof are hereby prohibited: . . . (d) The introduction or delivery for introduction into inter-state commerce of any article in violation of section . . . 505."

If scientific developments should result in a re-evaluation by qualified experts and a reversal of their recognition of safety. FDA could proceed in the District Court against the drug on the ground that it had again become a new drug under Section 201(p). Moreover, if the agency believes that the claims of effectiveness for an exempt drug are false or misleading it can proceed against them under Section 502(a) of the Act. There is no exemption from such proceeding.

FDA is therefore not without effective remedies. The fact that it cannot challenge the status of drugs such as Lutrexin under Section 505(e)(3) with respect to old claims of effectiveness results from a deliberate choice of the Congress.

IV

LUTREXIN IS EXEMPT FROM THE EFFECTIVENESS REQUIREMENTS OF THE 1962 AMENDMENTS BY REASON OF SECTION 107(c)(4) OF THOSE AMENDMENTS.

Section 107(c)(4) of the 1962 Amendments (J.A. 482) makes the effectiveness requirements of the amendments inapplicable to drugs which on or before October 9, 1962, (A) were being commercially used or sold in the United States, (B) were not "new drugs" and (C) were not then "covered by an effective [new drug] application, *"if the labeled conditions of use are the same as on that date."*

This provision protects a drug which meets the three conditions, not only from administrative withdrawal of approval of its NDA under Section 505(e)(3) of the Act but also from seizure, criminal or injunctive proceedings, instituted on the ground that the drug fails to comply with the effectiveness requirements of the 1962 Amendments. New claims, however, are not protected.

There is no doubt that Lutrexin meets the criterion of Clause A of Section 107(c)(4), i.e., that the drug was commercially used or sold in the United States on October 9, 1962. We believe that the literature and annexed affidavits (J.A. 87 et seq.; 32 et seq.) support our view that it was not a "new drug" (Clause B) on that date because it was generally recognized as safe and had been used to a material extent and for a material time within the meaning of Section 201(p)(2) as then written. If the court does not accept our view based on the record, we submit that no determination can be made on the matter without a hearing before FDA at which witnesses, including members of the NAS-NRC panel which evaluated the drug, may appear for examination and the evidence can be analyzed.

In our view also, Lutrexin was not "covered by an effective application" on October 9, 1962, within the meaning of Clause (C) of Section 107(c)(4) since, contrary to the FDA theory, there was no "effective" application at that time and consequently the drug could not have been "covered."

The Court of Appeals held that Lutrexin was not exempt under Section 107(c)(4) of the 1962 Amendments because approval of its NDA had not been withdrawn by FDA under Section 505(e). This construction distorts the purpose and effect of Section 505(e) and makes Section 107(c)(4) virtually meaningless.

The *purpose* of Section 505 (e) is to prevent the further shipment of a new drug in interstate commerce based upon a finding that it is unsafe or ineffective or otherwise fails to conform to the standards set up in Section 505 (e). Obviously, this purpose is entirely inconsistent with the effect which the court attributes to such withdrawal, *viz.*, that it operates as a condition of the exemption of the drug under Section 107(c)(4).

Thus, the bizarre result of the court's ruling would be that such a drug (including Lutrexin) could become exempt by reason of withdrawal of approval under Section 505(e), whereas the intended effect under the statute is to prevent the shipment of the drug in interstate commerce on the basis of the FDA view that it is still a new drug which does not comply with Section 505.

A construction so clearly inconsistent with the purpose of the statute should not be allowed to stand.

Our position that a drug which was no longer "new" (within the meaning of Section 201(p)(2) and Clause (B) of Section 107(c)(4) of the 1962 Amendments), was not "covered by an effective application" under Clause (C) of Section 107(c)(4), was rejected by the Court of Appeals in *USV*[23] on the ground that it would make surplusage of Clause (C).

By the same token, if, as FDA maintains, and the Court of Appeals agreed, every drug which had gone through the new drug procedures and had thereafter ceased to be a new drug was nevertheless "covered by an effective application" within the meaning of Clause (C), then Clause (B) would be surplusage; for if such a drug is "covered by an effective application" despite having lost its new drug status, the test of whether it is no longer a new drug (Clause (B)) would be useless.

A drug which was a "new drug" on October 9, 1962 (Clause (B)) could not be "covered by an effective application" (Clause (C)) if no NDA had been filed for it or if an NDA had been filed but had not been permitted to become effective under the Act before its admendment in 1962. These, then, are other situations in which either Clause (B) or (C) would be surplusage.

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[23] *USV Pharmaceutical Corporation* v. *Richardson*, 461 F.2d 223, J.A. 469-470.

It is the Government's position, as we have noted, that every drug which has gone through the new drug procedures and thereafter ceased to be a new drug is nevertheless "covered by an effective application" within the meaning of Clause (C) of Section 107(c)(2) of the 1962 Amendments and that this principle even extends to "me-too" [24] drugs despite the fact that the "me-toos" were never the subject of NDAs.

The Fourth Circuit stated in *USV* with respect to Section 107(c)(4): "The Congress never intended that a drug being marketed under an approved NDA might qualify under the 'grandfather clause.' This is plain from the comment of the Conference Committee Report that the exemption was to apply 'to existing labeling claims of drugs that have never previously been subject to the new-drug procedure.'" J.A. 470, 461 F.2d 223 at 227. It is our position that, since Lutrexin was no longer a new drug on October 9, 1962, it was not then being marketed under an NDA.

This approach of the Government and the Court of Appeals seems to render meaningless the term "effective application" as used both in Sections 107(c)(2) and 107(c)(4)(C) and would defeat the intention of Congress to exempt some drugs from the effectiveness provisions of the 1962 Amendments.

Thus, if every drug which has gone through the new drug procedures and all "me-too" drugs are "deemed approved" because their NDAs were allegedly "effective" on October 9, 1962, apparently no drug could meet the condition of Clause (C) of Section 107(c)(4) of the amendments that it be "not covered by an effective application," except a new drug (other than a "me-too" drug) for which no NDA has ever been filed.

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[24] Drugs which were copies of drugs which were the subject of NDAs but then became "old drugs," thereby making unnecessary the filing of NDAs for the copies.

The Government leans upon the statement of President Kennedy that a principal purpose of the amendments which he proposed to S. 1552, then pending (August 6, 1962) was: "to assure the American people that any drug on the market today is safe and effective for its intended use." The President's proposal, as presented by Senator Kefauver, and as it appeared in the original Harris bill (HR 11581), provided for the revocation of the effectiveness of an NDA if the Secretary finds—

> "(1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe or ineffective, *or show that there is substantial doubt as to the safety or effectiveness of such drug . . .*"[25] (Emphasis supplied)

This is *not* the provision adopted by the Committee. The provision adopted by the Committee and passed by the Congress is Section 505(e) which provides for withdrawal of "approval" if the Secretary finds, after due notice and opportunity for a hearing, that—

> "(3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have . . .

Even a cursory comparison of the two revocation provisions reveals that this one is vastly more restrictive upon the Secretary than that recommended by the President and Senator Kefauver. As Senator Hruska said of suspension of an application on the basis of "substantial doubt" as proposed by the President and Senator Kefauver—

> "However, 'substantial doubt' is a slippery, elastic term, permitting suspension whenever the Secretary

[25] 108 Cong. Rec. 16230, August 22, 1962.

> feels like it, without hope of meaningful judicial review" [26]

Apparently the Government interprets §§ 107(c) and 505(e)(3) as if the provision proposed by Senator Kefauver had been enacted into law, whereas, to the contrary, the Kefauver proposal was rejected by the Committees of both the Senate and the House and by those bodies themselves. Even if the proposals had been accepted it is difficult to see how that fact would support the proposition of the Government which would subject every drug which had ever gone through the new drug procedure to re-evaluation as to efficacy.

Complementing the basic considerations above discussed is the circumstance that the language of §§ 107(c)(3)(A) and (4) of the Amendments leads clearly to the conclusion that only *new claims* of effectiveness for old drugs whose NDAs became effective prior to October 10, 1962, were subject to the amendments. This view is supported by the legislative record of S. 1552, which, as revised, became the 1962 Amendments.

When the bill, as originally reported by the Senate Judiciary Committee, was changed to expand the definition of "new drug" to include drugs not generally recognized as effective, the Committee stated—

> "A question arose as to the circumstances and extent to which a *new claim or change of claim* of effectiveness made after the initial approval of a new drug application could be made without supporting evidence to be submitted to the Department under the new-drug procedure. In order to eliminate any possible ambiguity on this point the term 'effectiveness' is employed in the committee's substitute amendment" (Emphasis supplied, S. Rep. No. 1744, Part II, 87th Cong., 2d Sess. 5).

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[26] 108 Cong. Rec. 10108, June 11, 1962.

Likewise, on the floor, Senator Eastland, consistently with the language of Sections 107(c)(2),(3) and (4), said that, with the addition of "effectiveness" to the definition "every brand new product, and every new claim for an existing product, would be subject to the tests and procedures established in § 505 of the Act" (108 Cong. Rec. 16304, August 23, 1962).

There is nothing inconsistent with these explanations in the history of HR 11581, the companion bill to S. 1552.

It must be clear from the legislative history as well as from the terminology of the 1962 Amendments themselves that statements in the Committee Reports and in debate relating to withdrawal of approval of NDAs on the grounds of lack of effectiveness after two years from October 9, 1962, referred only to withdrawal of approval of NDAs for drugs which were still *new drugs* on that date.

It is our view that a provision of this nature, concededly not artfully drafted, should not be construed to deny effect to Congress' undoubted intention to exempt some drugs from certain obligations under the 1962 amendments. Yet that is the effect of the decision of the Fourth Circuit. FDA would go even further and deprive the provision of any practical effect at all.

We do not claim that the language and legislative history of the Drug Amendments of 1962 is crystal clear in all respects. In fact, Senator Kefauver, an active sponsor of the bill which became the 1962 Amendments stated—

> "Those in the future who attempt to study the legislative history of this measure as it passed through its various stages may be forgiven if they become somewhat confused. In my experience there have

been few bills which have had so varied a legislative history." [37]

We do maintain, however, that the language of the amendments and their history evince a purpose by Congress to exempt some drugs, such as Lutrexin entirely from the effectiveness provisions of the amendments except for new claims.

This does not mean that judicial remedies are not available to FDA to deal with such drugs in matters other than the effectiveness requirements of the 1962 Amendments. All such remedies may properly be invoked and no new claims of effectiveness (any not in use on October 9, 1962) are exempt under Section 107(c)(4).

V

CONCLUSION

The New Drug Application for Lutrexin was not "deemed approved" under the provisions of Section 107(c)(2) of the Drug Amendments of 1962 and is therefore not subject to *administrative* withdrawal proceedings under Section 505(e)(3) of the Act as amended, based on allegations of a lack of substantial evidence of effectiveness to support old claims for the drug, i.e., claims which were being made as of October 9, 1962.

Moreover, Lutrexin is entitled to the broader exemption provided by Section 107(c)(4), from *any* legal proceedings based on the effectiveness requirements of the 1962 Amendments. The exemption does not extend to other legal proceedings under the Act.

HW&D is entitled to an administrative hearing before FDA on the question of whether FDA has jurisdiction despite the provisions of Sections 107(c)(2) and

[37] 108 Cong. Rec. 22037, October 3, 1962.

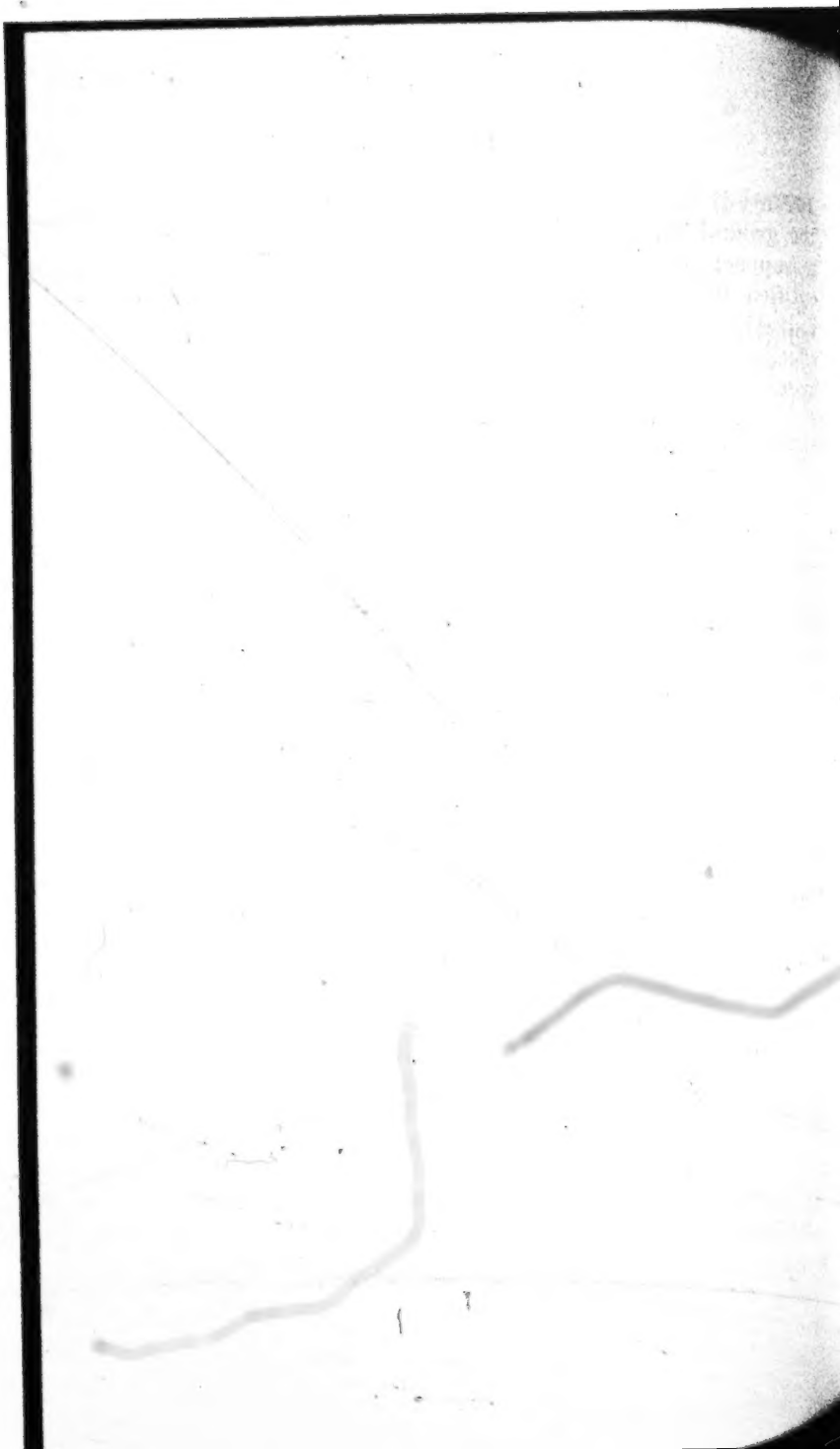
107(c)(4) to withdraw the old NDA for Lutrexin on the ground that there is a lack of substantial evidence to support the old claims for its effectiveness. It is also entitled to such a hearing on the question of whether Lutrexin is now generally recognized as both safe *and* effective and therefore not subject to FDA's jurisdiction under any provision of Section 505.

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-528

CIBA CORPORATION, a corporation of the State of Delaware,

Petitioner,

vs.

ELLIOTT L. RICHARDSON, Secretary of Health, Education and Welfare and DR. CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Respondents.

BRIEF FOR THE PETITIONER

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IN THE

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No. 72-528

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Petitioner,

vs.

ELLIOTT L. RICHARDSON, Secretary of Health, Education and Welfare and DR. CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Respondents.

BRIEF FOR THE PETITIONER

Opinions Below

The opinion of the Court of Appeals appears at 463 F.2d 225 (3rd Cir. 1972) and in the appendix at p. 215. The oral opinion of the District Court is set forth in the appendix at pp. 208-14.

Jurisdiction

The judgment and opinion of the Court of Appeals were entered on June 5, 1972. By order signed by Justice Rhenquist of this Court dated September 1, 1972, the time for filing a petition for a writ of certiorari herein was extended

to October 2, 1972, and the petition was filed on that date and granted on January 8, 1973. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

Statute Involved

The statute involved is the Food, Drug and Cosmetic Act of 1938, as amended, 21 U.S.C. § 301 *et seq.* The pertinent sections of that Act are set forth in the appendix at p. 475.

Question Presented

Do the Federal district courts have exclusive jurisdiction to adjudicate whether a drug is a "new drug" as defined in the Food, Drug and Cosmetic Act of 1938, as amended, and therefore subject to the regulatory procedures applicable to such drugs?

Statement of the Case

The Federal Food, Drug and Cosmetic Act of 1938,[1] as amended (the "Act"), prohibits the shipment in interstate commerce of any "new drug" not covered by an approved New Drug Application. Approval of a New Drug Application is granted or denied by the Food and Drug Administration (the "FDA") on the basis of information submitted by the manufacturer in the New Drug Application. Under the Act, the New Drug Application is approved upon a showing that the "new drug" is safe and effective for the conditions of use recommended or prescribed in its labeling.

Not all drugs, however, require an approved New Drug Application for marketing. Only if a drug is not generally

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[1] 21 U.S.C. § 301 *et seq.*

recognized as safe and effective for the conditions of use recommended or prescribed in its labeling is it a "new drug" and thus required to be covered by an approved New Drug Application.

Prior to 1962 a drug was a "new drug" only if not generally recognized as safe, and a manufacturer's New Drug Application was only required to contain evidence of the drug's safety. The amendments to the Act in 1962[2] changed the definition of "new drug" to encompass drugs not generally recognized as safe and *effective,* and added to the grounds for New Drug Application approval the requirement of the production of evidence of the effectiveness of a "new drug" as well as of its safety. Because of this new requirement, the FDA contracted the National Academy of Sciences-National Research Council (the "NAS-NRC") for the review of drugs subject to New Drugs Applications prior to 1962 to determine whether there existed for such drugs the requisite evidence of their effectiveness.

A New Drug Application for Ritonic, the drug which is the subject of this action, became effective on January 12, 1958, based upon proof of safety. On September 12, 1969, the FDA notified petitioner of its intention to withdraw the approval of the Ritonic New Drug Application on the grounds that the NAS-NRC review of Ritonic had concluded that there was not substantial evidence of its effectiveness and requested the submission of additional evidence of its efficacy.[3] By letter dated October 10, 1969, petitioner indicated its disagreement with the NAS-NRC conclusion of lack of substantial evidence that Ritonic is effective. In addition petitioner expressly reserved its right to assert that Ritonic was not a "new drug" and therefore not subject to the New Drug Application approval requirements of the Act.[4]

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[2] 76 Stat. 780 (1962).

[3] Appendix p. 199.

[4] Appendix p. 202.

Before any action was taken to withdraw the FDA's approval of Ritonic, the Pharmaceutical Manufacturers Association filed a suit challenging the validity of the regulations establishing the procedures to be followed in determining the efficacy of drug products. That action was determined adversely to the FDA on January 16, 1970, *Pharmaceutical Manufacturers Association* v. *Finch*, 307 F.Supp. 858 (D.Del. 1970), and on May 8, 1970, the FDA repromulgated the regulations.[5]

On August 5, 1970, the FDA issued a formal notice of its intention to withdraw its approval of the New Drug Application for Ritonic pursuant to the new regulations.[6] That notice afforded petitioner an opportunity to request a hearing to show substantial evidence of the safety and efficacy of the product. By letter dated August 31, 1970,[7] petitioner requested a hearing but indicated its disagreement with the regulation of the FDA pursuant to which it sought to require petitioner to state reasons why the New Drug Application should not be withdrawn as a precondition to a hearing.[8] Petitioner again reserved its right to maintain that the product in issue was not a new drug.[9]

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[5] 21 C.F.R. §§ 130.12, 130.14.

[6] Appendix p. 203.

[7] Appendix p. 206.

[8] This position was based on the arguments being advanced in the courts by the PMA in an action against the FDA. That action was decided adversely to PMA on October 20, 1970, *Pharmaceutical Manufacturers Association* v. *Elliott L. Richardson*, 318 F.Supp. 301 (D.Del. 1970).

[9] Petitioner stated in its response:

> "We wish to advise you that it is CIBA's position that Ritonic Capsules are not now a new drug under the Food, Drug and Cosmetic Act, as amended and that the amendments of 1962 are not applicable to that drug. Therefore, this election to avail ourselves of the opportunity for a Hearing is made with a reservation of the right to establish these facts in the administrative proceedings, or in judicial proceedings, or both."

On September 4, 1970, this action was instituted. Several weeks later the FDA published a notice withdrawing its approval of the New Drug Application for Ritonic[10] without addressing itself to petitioner's position that Ritonic was not a "new drug."

As a result of the denial of the requested hearing and because there was no appellate decision considering and sustaining the validity of the republished regulations, petitioner filed a direct appeal under Section 505(h) of the Act. In that appeal petitioner challenged the right of the FDA to condition the manufacturer's right to a hearing upon submission of evidence which it might consider to be substantial. The action of the FDA in this instance was affirmed. *Ciba-Geigy Corporation* v. *Richardson,* 446 F.2d 466 (2nd Cir. 1971). That appeal did not, and, for reasons set out hereinafter, could not have considered whether Ritonic is a "new drug."

The FDA moved to dismiss the complaint in this case on the ground, *inter alia,* that the FDA, not the courts, has exclusive jurisdiction to determine whether a drug is a "new drug" and that a manufacturer's only avenue of judicial redress from an FDA determination on this point is by appeal to a circuit court of appeals By stipulation of the parties, this jurisdictional question was the sole issue briefed or argued in the district court.

The district court dismissed the action on the ground that even if that court had jurisdiction it would exercise its discretion and refuse to determine whether Ritonic was a "new drug" in a declaratory judgment action.[11] The Third Circuit Court of Appeals affirmed the dismissal on the ground that the FDA has primary jurisdicton to adjudicate whether a drug is a "new drug" and that the FDA

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[10] Appendix p. 207.

[11] Transcript of Oral Argument, Appendix pps. 208-14.

properly exercised that jurisdiction in its administrative proceeding withdrawing the New Drug Application previously in effect for Ritonic.

ARGUMENT

The District Court Has Sole Jurisdiction To Adjudicate Whether a Drug Is a "New Drug" Within the Meaning of the Act.

The Act provides that before a manufacturer may ship a "new drug" in interstate commerce it must obtain FDA approval of a New Drug Application for that drug.[12] The FDA is instructed to issue an order denying approval of a New Drug Application[13] or withdrawing approval previously granted[14] if the Commissioner concludes that there is a lack of "substantial evidence" that the drug involved is safe and effective for the conditions of use prescribed or recommended in its labeling.

"Substantial evidence" is a term of art referring to particular types of scientific evidence set out in the Act and the regulations promulgated thereunder.[15] In essence, "substantial evidence" involves the results of "adequate and well-controlled clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."

Before issuing an order denying or withdrawing its approval of a New Drug Application, the FDA must give a manufacturer notice and opportunity for an adminis-

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[12] Act § 301(d) which incorporates by reference § 505(a); 21 U.S.C. 331(d), 355(a); Appendix pps. 475, 478.

[13] Act § 505(d); 21 U.S.C. 355(d); Appendix p. 478.

[14] Act § 505(e); 21 U.S.C. 355(e); Appendix p. 479.

[15] Act § 505(d); 21 U.S.C. 355(d); Appendix p. 478; 21 C.F.R., Part 130, § 130.12.

trative hearing.[16] After final FDA action denying or withdrawing approval of a New Drug Application, a manufacturer is entitled to seek a review of the FDA's action in an appropriate court of appeals.[17]

Not all drugs, however, are required to have an approved New Drug Application before they can be marketed; only "new drugs" must follow this procedure. The term "new drug" is also a term of art defined in the Act.[18] In essence a "new drug" is any drug which is not generally recognized by experts qualified to evaluate the safety and effectiveness of drugs as being safe and effective for the conditions of use recommended in its labeling or any drug which is so recognized but which has not been used to a material extent or for a material time for the conditions recommended in its labeling.

The distinction between whether a drug is a "new drug", i.e., not generally recognized as safe and effective, and required to have a New Drug Application, and whether a "new drug" has been demonstrated by "substantial evidence" to be safe and effective and therefore entitled to approval of its New Drug Application is part of the basic structure of the Act. If a drug has been in use by the medical profession for a material time and to a material extent and if, through such use, has become generally recognized as being safe and effective, then the drug is no longer a "new drug" and the manufacturer may market it without first obtaining an approved New Drug Application.

Respondents do not dispute that drugs which are not "new drugs" may be legally marketed without an approved New Drug Application; they argue, instead, that the FDA

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[16] Act §§ 505(d); 505(e); 21 U.S.C. 355(d); 355(e); Appendix pps. 478-479.

[17] Act § 505(h); 21 U.S.C. 355(h); Appendix p. 480.

[18] Act § 201(p); 21 U.S.C. 321(p); Appendix pps. 482-83.

rather than the district courts has jurisdiction of the "new drug" question. They contend that, when the FDA has made a determination of this question in connection with the withdrawal of a New Drug Application, the only judicial remedy is an appeal from its action to an appropriate court of appeals. Respondents do not and cannot, however, point to anything in the Act granting the FDA the jurisdiction claimed.

Section 505 of the Act, the section establishing power in the FDA to regulate "new drugs", particularly parts (d) and (e) thereof, states that if, after notice and opportunity for a hearing, the Commissioner determines that a New Drug Application does not contain adequate proof of safety and effectiveness, he shall "issue an order refusing to approve the application" or "withdraw approval of an application" granted previously.

Nowhere do sections 505(d) and (e) (or any other sections) authorize the Commissioner to adjudicate whether a drug has been in use for a material time and to a material extent or whether it is generally recognized as safe and effective. Neither does the Act empower the Commissioner to issue an order declaring the drug is or is not a "new drug". The administrative procedure which these sections create clearly contemplates only the adjudication of whether the tests for approval of a New Drug Application, i.e., "substantial evidence" of safety and effectiveness, have been met.

Further evidence of this clearly defined role of the FDA is found in Section 505(h) of the Act which specifies the limits of the review jurisdiction of the federal circuit courts. Section 505(h) provides for an appeal by a manufacturer from a determination in the administrative proceeding created by Sections 505(d) and (e) denying or withdrawing New Drug Application approval. The language of this section makes clear, however, that it does not

empower the circuit courts to review a finding that a drug is a "new drug." In pertinent part this section reads as follows:

> "(h) An appeal may be taken by the applicant from an order of the Secretary *refusing or withdrawing approval of an application* [for approval of a New Drug Application] under this section. Such appeal shall be taken by filing in the United States Court of Appeals . . . a written petition praying that the order of the Secretary [withdrawing or denying approval of the New Drug Application] be set aside." (Emphasis added)

This section only gives the circuit courts appellate jurisdiction over the Secretary's action refusing or withdrawing approval of a new drug application. The circuits courts, therefore, do not have appellate jurisdiction with respect to the "new drug" issue since, like an administrative agency, they have only that jurisdiction granted to them by statute. See *Turkel* v. *FDA*, 334 F.2d 844 (6th Cir. 1964), where the FDA argued, and the court held, that appellate jurisdiction is dependent wholly upon statute and the applicable statute, § 505(h) of the Act, only grants a right of appeal from the denial or withdrawal of a New Drug Application.

Although jurisdiction to adjudicate which drugs are "new drugs" is not given to the FDA, it is implicit from the Act that such jurisdiction does lie in the federal district courts. The Act creates severe penalties, including fining and imprisonment of a manufacturer's officers and seizure of its product in interstate commerce, if such manufacturer ships a "new drug" in interstate commerce without an approved New Drug Application.[19] For these penalties to be imposed, the FDA must institute appropriate proceed-

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[19] Act §§ 302, 303(a), 304(a); 21 U.S.C. 332, 333(a), 334(a); Appendix pps. 475-76.

ings in a federal district court and, in such proceeding, the manufacturer will be guilty of no offense if its drug is found to be not a "new drug."[20]

The district court's jurisdiction to adjudicate whether the drug involved is a "new drug" has been consistently recognized in enforcement proceeding cases for many years. The question adjudicated in these cases is not whether the drug is actually safe and effective, a question which would involve an analysis of scientific and medical evidence particularly within the competence of the FDA. Rather, the inquiry is what the consensus is among doctors and others in a positon to be familiar with the drug's safety and effectiveness. This issue is readily within the competence of the courts. See e.g., *Merritt Corp.* v. *Folsom*, 165 F.Supp. 418 (D.D.C. 1958); *U.S.* v. *345 Bulk Cartons . . . "Trim Reducing Aid Cigarettes"*, 178 F.Supp. 847 (D.N.J. 1959); *U.S.* v. *An Article of Drug . . . "Quinaglute,"* 268 F.Supp. 245 (E.D.Mo. 1967); *U.S.* v. *Articles of Drug . . . "Quick-O-Ver,"* 274 F.Supp. 443, 445-46 (D.Md. 1967); *U.S.* v. *An Article of Drug . . . "Line Away"*, 284 F.Supp. 107 (D.Del. 1968) affirmed other grounds 415 F.2d 369 (3rd Cir. 1969); *U.S.* v. *7 Cartons . . . "Ferro-Lac"*, 293 F.Supp. 660 (S.D. Ill. 1968) affirmed 424 F.2d 1364 (7th Cir. 1970); *U.S.* v. *An Article of Drug . . . "Furestrol"*, 294 F.Supp. 1307 (D.Ga. 1969) affirmed 415 F.2d 390 (5th Cir. 1969); *U. S.* v. *An Article of Drug . . . "Excedrin P.M."*, —— F.Supp. ——, CCH, Food Drug and Cosmetic Law Reporter, ¶ 40,486 (E.D.N.Y. 1971); *U.S.* v. *An Article of Drug . . . "Bentex Ulcerine," etc.*, —— F.Supp. —— (D.Tenn. 1972), affirmed —— F.2d ——, CCH, Food Drug and Cosmetic Law Reporter ¶ 40,771 (5th Cir. 1972). See also *U.S.* v. *Allan Drug Corp.*, 357 F.2d 713 (10th Cir. 1966).

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[20] Act § 301(d) incorporating by reference Section 505(a); Appendix pps. 475, 477.

Once it is established that the district courts have jurisdiction to determine the "new drug" issue in enforcement proceedings, it is axiomatic that they must also have jurisdiction to decide this issue in a declaratory judgment action instituted by a manufacturer. The only difference between the two actions is that in the declaratory action the manufacturer seeks to have its product's "new drug" status determined prior to being forced to incur the risk of being subject to criminal and seizure penalties if it does not prevail in the enforcement action. See *Abbott Laboratories* v. *Gardner*, 387 U.S. 136, 18 L.ed 2d 681 and *Gardner* v. *Toilet Goods Association*, 387 U.S. 167, 18 L.ed 2d 704 (1967). Jurisdiction of the "new drug" question has also been assumed by the courts in a number of recent declaratory judgment actions. See *e.g.*, *USV Pharmaceutical Corporation* v. *Richardson*, —— F.Supp. ——, CCH, Food Drug and Cosmetic Law Reporter ¶40,489 (E.D. Va. 1971), affirmed —— F.2d —— (4th Cir. 1972); *Lemmon Pharmacal Co.* v. *Elliott L. Richardson, et al.*, 319 F.Supp. 375 (E.D. Pa. 1970). See also *AMP, Inc.* v. *Gardner*, 389 F.2d 825 (2nd Cir. 1968), affirming 275 F.Supp. 410 (S.D.N.Y. 1967).

Not only is the decision of the court below that FDA has primary jurisdiction to adjudicate the "new drug" status of drugs devoid of statutory or judicial support, it also is contrary to the settled interpretation of the Act given to it by the FDA and the drug industry since its enactment in 1938. Petitioner knows of no instance in which the FDA has claimed jurisdiction of this question prior to the claims made in the briefs filed on its behalf in this and several similar actions commenced at approximately the same time.

From the series of notices issued by the FDA prior to its withdrawal of the Ritonic New Drug Application, it is clear that the Agency even then did not contemplate taking evidence or granting a hearing on the "new drug" status of Ritonic. The initial notice of the results of the NAS-NRC

report on Ritonic invited Ciba to submit evidence bearing on why the New Drug Application should not be withdrawn. It stated that "the only material which will be considered acceptable for review must be well organized and consist of adequate and well-controlled studies bearing on the efficacy of the products and not previously submitted." That is, the only acceptable submission would be "substantial evidence" in support of the drug's effectiveness and bearing on the question whether or not to withdraw the New Drug Application, not evidence as to the general recognition of the drug's effectiveness. Similarly, the notice of opportunity for a hearing only contemplated a hearing on the question of the withdrawal of the New Drug Application and conditioned the right to that hearing on the presentation of the "clinical and other investigational data" Ciba was prepared to prove in support of its New Drug Application.

Further evidence of the FDA's previous (and possibly current) view on this question is the fact that it has never attempted to promulgate regulations dealing with the type of evidence acceptable for a determination of a drug's "new drug" status or the criteria for obtaining a hearing on this issue. This omission is all the more significant since the FDA promulgated regulations in September of 1969 and again in May of 1970[21] setting out the types of evidence and the hearing procedures applicable in connection with the withdrawal of New Drug Applications.

It is a fundamental principle of statutory interpretation that a continuous interpretation of a statute by the parties which it affects, and particularly by the executive agency created to implement it, will be given great weight in the interpretation of that statute and not overturned in the

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[21] 21 C.F.R. §§ 130.12, 130.14.

absence of cogent reasons therefore. See *e.g., United States* v. *Midwest Oil Co.*, 236 U.S. 459, 472-473, 59 L.ed. 2d 673, 681 (1915); *McLaren* v. *Fleischer*, 256 U.S. 477, 480-481, 65 L.ed. 1052, 1053 (1921); *Bowles* v. *Seminole Rock Co.*, 325 U.S. 410, 413-414, 89 L.ed. 1700, 1702 (1945); *Power Reactor Co.* v. *International Union of Electrical, etc.*, 367 U.S. 396, 408, 6 L.ed. 2d 924, 932 (1961); 82 C.J.S., Statutes § 359; 2 Sutherland, *Statutes and Statutory Construction*, (1943) § 5105. In *Midwest Oil Co., supra*, this Court stated that this presumption is

> "the basis of a wise and quieting rule that, in determining the meaning of a statute or the existence of a power, weight shall be given to the usage itself,—even when the validity of the practice is the subject of investigation."

In sharp contrast to the conclusion of the court below, the Court of Appeals for the Fourth Circuit, in *Bentex Pharmaceuticals, Inc.* v. *Richardson*, 463 F.2d 363, (4th Cir. 1972), appendix p. 258, in a carefully reasoned opinion has rejected the argument of the FDA advanced below and concluded that the FDA is without jurisdiction to adjudicate whether a drug is a "new drug."

The *Bentex* case, like the instant one, was a declaratory judgment action commenced by a manufacturer seeking a determination that its product was not a "new drug." The manufacturer in *Bentex*, like Ciba, acted after receiving notice from the FDA that it had determined its product to be a "new drug" which lacked an approved New Drug Application and which would be subject to FDA instituted enforcement proceedings if not withdrawn from the market. In *Bentex* the FDA argued, as it did below, that it, rather than the courts, has primary jurisdiction to adjudicate the "new drug" status of drugs.

The Fourth Circuit recognized that the questions of whether to grant approval of a New Drug Application and

whether a drug is a "new drug" are wholly sepa
distinct. After an analysis of the Act, it held th
was no basis for concluding that the FDA had juri
to adjudicate the latter question or that the co
appeals would have jurisdiction on appeal to revie
determination if it were made.

It is submitted that the conclusion reached by the
Circuit is consistent with the language of the A
judicial and historic administrative interpretatio
manufacturers are entitled to an impartial judicial
for an adjudication of the "new drug" question.

CONCLUSION

For the foregoing reasons it is respectfully sub
that the opinion and judgment of the Third Circuit
of Appeals should be reversed and that this matter
be remanded to the district court for a determinat
whether Ritonic is a "new drug".

Respectfully submitted,

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In the Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-555

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, PETITIONERS

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

BRIEF FOR PETITIONERS

OPINIONS BELOW

The opinion of the court of appeals (J.A. 258-270[1]) is reported at 463 F. 2d 363. The opinion of the district court (J.A. 251-258) is not officially reported.

JURISDICTION

The judgment of the court of appeals (J.A. 270) was entered on May 23, 1972. Mr. Justice Rehnquist extended the time within which to file a petition for

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[1] "J.A." refers to the Joint Appendix filed by the parties in this case and in Nos. 72-394, 72-414, 72-528, and 72-666, with which this case has been consolidated.

a writ of certiorari to October 5, 1972. The petition was filed on that date and was granted on January 8, 1973 (J.A. 271). The jurisdiction of this Court rests on 28 U.S.C. 1254(1).

QUESTION PRESENTED

Whether the Food and Drug Administration has jurisdiction to determine initially whether a product is a "new drug" which must be administratively approved as safe and effective before it can be sold in commerce.

STATUTES INVOLVED

Relevant provisions of the Federal Food, Drug, and Cosmetic Act, 52 Stat. 1040, as amended by the Harris-Kefauver Act, 76 Stat. 780, 21 U.S.C. 301 *et seq.*, and of the Administrative Procedure Act, 5 U.S.C. 551–559, 701–706, are set forth in the Joint Appendix (J.A. 475–487).

STATEMENT

This is one of five consolidated cases now pending before the Court involving the interpretation of, and the procedures to be followed in implementing, the effectiveness provisions of the 1692 amendments to the Federal Food, Drug, and Cosmetic Act of 1938 (76 Stat. 780–786).[2] These five cases present interrelated

[2] The other cases are: *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, No. 72–394; *Hynson, Westcott and Dunning, Inc.* v. *Weinberger*, No. 72–414 (cross-petition); *CIBA Corporation* v. *Weinberger*, No. 72–528; and *USV Pharmaceutical Corporation* v. *Weinberger*, No. 72–666. On January 8, 1973, this Court granted the petitions for writs of certiorari in all five cases, consolidated them, and allotted a total of three hours for argument.

and overlapping issues. We are therefore setting forth, in this brief, a general discussion of the historical background of drug marketing regulation, the statutes involved, and the efforts of the Food and Drug Administration ("FDA") to implement the congressional directives relating to drug efficacy, in order to provide a background against which the issues involved in all five cases may be assessed.

I. STATUTORY AND ADMINISTRATIVE BACKGROUND

A. THE FEDERAL FOOD, DRUG, AND COSMETIC ACT OF 1938

Until 1938, federal law did not provide for any kind of administrative pre-marketing approval for pharmaceuticals sold in interstate commerce. The Food and Drug Act of 1906, 34 Stat. 768, prohibited introduction into commerce of adulterated and misbranded drugs, narrowly defined, and provided only criminal sanctions and seizure by libel for condemnation. The Secretary of Agriculture was authorized to conduct hearings concerning particular products, but only for the purpose of certifying violations to the United States Attorney.

In 1938, however, spurred by a tragedy resulting from the marketing of an untested, toxic drug,[3] Con-

[3] The product was "Elixir Sulfanilamide." The manufacturer combined sulfanilamide, a useful drug usually administered in tablet or powder form, with diethylene glycol, an extremely toxic solvent (now used mainly as antifreeze). The company marketed this new product without first testing it for safety. During September and October of 1937, at least 73 persons died as a direct result of taking "Elixir Sulfanilamide." Dunn, *Federal Food, Drug and Cosmetic Act* (1938), pp. 1316–1327; S. Doc. No. 124, 75th Cong., 2d Sess. (1937).

gress provided in the Federal Food, Drug and Cosmetic Act, 52 Stat. 1040, for regulatory clearance of drugs prior to marketing[4] and for administrative suspension of such clearance if thereafter required for public safety. The statute established a scheme which prohibited the introduction of "any new drug" in interstate commerce unless an application filed with the Secretary of Agriculture[5] was "effective with respect to such drug." Section 505(a), 52 Stat. 1052.[6] Such "new drug applications" are known as "NDAs". A "new drug" was defined as "[a]ny drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe" for its intended use. Section 201(p), 52 Stat. 1041–1042.[7] The application was automatically to become effective within a fixed period unless the Secretary, after notice and opportunity for hearing, refused to permit it to become effective after finding that he could not determine from existing evidence,

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[4] See H. Rep. No. 2139, 75th Cong., 3d Sess. (1938); Dunn, *supra*, at 817, 823.

[5] The functions of the Secretary of Agriculture under the Act were assigned to the Food and Drug Administration, which was transferred in 1940 to the Federal Security Agency, and in 1953 to the Department of Health, Education and Welfare. The Secretary of the latter Department has delegated his authority under the Act to the Commissioner of Food and Drugs. 21 C.F.R. 2.120. See note following 21 U.S.C. 321 at p. 5421.

[6] Sections 201(p) and 505(a)–(e) of the 1938 Act are set forth at J.A. 482–484.

[7] A grandfather clause exempted drugs subject to the 1906 Act whose labeling had not been changed. Section 201(p)(1), 52 Stat. 1042.

or had not been shown, that the drug was safe. Sections 505(c) and (d), 52 Stat. 1052. Any NDA in effect could be suspended, after notice and opportunity for hearing, if clinical experience or new testing methods showed that the drug was not safe. Section 505(e), 52 Stat. 1053. Orders denying or suspending an NDA were reviewable on the administrative record in the district courts. Section 505(h), 52 Stat. 1053.

This regulatory authority was supplemented by the Act's general administrative provisions authorizing the Secretary to promulgate regulations for the efficient enforcement of the Act, and to conduct examinations, inspections and investigations and publish the results. Sections 701–705, 52 Stat. 1055–1058. In addition, judicial sanctions were authorized to enforce the Act's administrative requirements. The marketing of a "new drug" without an effective NDA could be enjoined or be made the basis of a criminal prosecution, or the drug involved could be seized in libel and condemnation proceedings.[8] The Act also provided for the same judicial sanctions to be applied to the sale of misbranded drugs—*i.e.,* drugs for which the labeling is false or misleading.[9]

B. FDA'S IMPLEMENTATION OF THE 1938 ACT AND THE "ME-TOO" PROBLEM.

The agency's administration of the Act was directly affected by three factors: the enormous number of

[8] Sections 301(d), 302(a), 303, 304 (21 U.S.C. (1958 ed.) 331(d), 332(a), 333, 334).

[9] Sections 502(a), 301(a), 302, 303, 304 (21 U.S.C. (1958 ed.) 352a, 331(a), 332(a), 333, 334).

new drug applications it was required to review, in relation to its limited resources; the absence of any requirement that manufacturers and packagers register drugs with the agency before or after putting them on the market; and FDA's lack of power, in determining whether to permit an NDA to become effective, to consider whether products which were safe were also therapeutically efficacious.

From the outset, the Food and Drug Administration received a swelling stream of new drug applications supported by voluminous data.[10] To cope with this problem, which was aggravated by war-related staff shortages, the agency adopted the practice in 1942 of examining each application to determine whether the product was in fact a new drug, and of advising the manufacturer of its determination. By 1949, the Commissioner was able to report that the "growing disposition on the part of the drug industry to ask the opinion of the Food and Drug Administration in advance as to the status of proposed new products * * * has led to a steady decline in applications ruled not new drugs."[11] Nevertheless, in the twenty-four years between 1938 and 1962 the number and total sales of "new drugs" on the market had grown enormously.[12]

[10] By June 30, 1939, the agency had received 1,277 NDAs. 1939 Annual Report of the Food and Drug Administration, reprinted in Federal Food, Drug, and Cosmetic Law Administrative Reports—1907–1949 (hereafter "Admin. Reps.") at 927; by 1941 the number filed had increased to 4,128. *Id.* at 1006.

[11] Admin Reps. at 1415.

[12] Expenditures for drugs increased from $1.8 billion in 1951 to more than $5 billion in 1962. Annual Reports of the U.S. Department of Health, Education, and Welfare (1961) at 315,

By June 30, 1962, the agency had permitted 9,457 NDAs to become effective, as well as some 12,000 supplemental NDAs for labeling, manufacturing and formulation changes on articles previously covered.[13]

In addition to products for which an NDA had become effective, however, there were many thousands of similar or identical formulations for which the manufacturer had not filed an application. These manufacturers either concluded that their products were generally recognized as safe because an NDA was in effect for the drug they imitated, marketed their products illegally without being discovered, or received an advisory opinion letter from the agency that an NDA was not required because their product was generally recognized among experts as safe.[14] Such products are known as "me-too" drugs.[15] While the precise number

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(1963) at 285. In 1954 the Secretary reported that: "In the drug field at least half of the drugs in prominent use today were unknown when the Food, Drug, and Cosmetic Act was enacted. All of the antibiotics and all but one of the sulfonamides have achieved their present widespread use since 1938. Whereas 10 million dollars' worth of endocrines were produced in 1939, the output had grown to $90 million in 1952, and new products such as cortisone and ACTH had entered the picture." Annual Report of U.S. Department of Health, Education, and Welfare (1954) at 193.

[13] See Annual Reports of the Federal Security Agency (1938–1952); Annual Reports of the U.S. Department of Health, Education, and Welfare (1953–1962). The Food and Drug Administration estimates that of the 5,737 NDAs that became effective between 1950 and 1962, approximately 1,500 were for veterinary products.

[14] Such "not new drug" letters were issued when one or more NDAs were already effective on similar drugs.

[15] See Hearings on Drug Listing Act, 1971, before the Senate Committee on Labor and Public Welfare, 92d Cong., 1st Sess., at 18, 21–22.

of all such identical or related drugs has not been ascertained, it was estimated in 1969 that for every NDA drug there are five identical or similar drugs.[16] FDA's experience to date indicates that this estimate is low. FDA has found an average ratio of 13 similar or "me-too" drugs for each NDA drug withdrawn from the market because of a lack of substantial evidence of effectiveness.

The legality of marketing "me-toos" without an effective NDA was questionable, at least in the absence of a "not new drug" letter from FDA, because the criteria for an effective NDA in Section 505(b) also required applicants to show that their manufacturing processes were adequately controlled. A number of products were seized because this had not been shown by the manufacturer, even though there were effective applications for the same drug when manufactured by others.[17] However, the agency's ability to prevent such products from being marketed was limited. A major part of its professional staff was continuously engaged in reviewing for safety the voluminous NDAs filed in

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[16] Hearings before the Subcommittee on Public Health and Welfare, House Committee on Interstate and Foreign Commerce, on FDA Consumer Protection Activities—FDA Reorganization, 91st Cong., 1st and 2d Sess., at 230.

Altogether, there are estimated to be about 35,000 prescription drug products on the American market. See Hearings on Present Status of Competition in the Pharmaceutical Industry before the Subcommittee on Monopoly of the Senate Select Committee on Small Business, 92d Cong., 2d Sess., Part 22, at 8510.

[17] Annual Report of U.S. Department of Health, Education and Welfare (1959) at 207.

the decade prior to 1962,[18] which it received at an average rate of more than one per day. Moreover, the law did not require manufacturers and packagers of drugs to register their products with the agency, and no general census of products on the market existed.[19] The agency therefore could not effectively police the market for "me-too" products except by occasional, almost random proceedings. In some instances, where the product and its labeling appeared virtually identical with products for which NDAs had become effective under the Act's safety standard, the agency's staff issued opinions advising that the products would not be treated as "new drugs" under the Act.[20]

Finally, the agency was hampered by its inability to proceed against drugs which were therapeutically ineffective. In 1939 the head of the agency, in reporting on applications that had become effective, noted

[18] In 1939, NDAs were filed containing as many as 2,000 case reports from 100 doctors investigating the safety, if not the effectiveness, of new drugs. Admin. Reps. at 927–928. By 1970, NDAs contained up to 250 volumes of data. The average NDA is about 30 volumes—a stack of data 10 to 12 feet high. Hearings on FDA Consumer Protection Activities—FDA Reorganization before the Subcommittee on Public Health and Welfare, House Committee on Interstate and Foreign Commerce, 91st Cong., 1st and 2d Sess., at 58, 146. Some NDAs now contain as many as 400 volumes of data.

[19] Not until 1972 did Congress adopt a Drug Listing Act, 86 Stat. 559.

[20] Admin Reps. at 1415. There are no data to show the number of drugs for which the agency issued "not new drug" letters. It is fair to say, however, that several thousand were issued. Annual Reports of U.S. Department of Health, Education, and Welfare (1963) at 312, (1964) at 301. This policy was abandoned in 1968. See p. 21, *infra*.

that "in many instances it is questionable whether they possess the therapeutic properties claimed for them," [21] and the agency's misgivings on the subject were reiterated as it gained experience.[22] Only by complex proceedings for mislabeling was the agency, on occasion, able to stop sale of a few ineffective products. In some instances involving drugs which were offered for treatment of life-threatening diseases, it was also able to consider effectiveness in relation to safety.[23]

C. THE HARRIS-KEFAUVER "EFFICACY AMENDMENTS" OF 1962

1. Legislative history

From late 1959 until mid-1961, the Senate Subcommittee on Antitrust and Monopoly, Committee on the Judiciary, conducted a study of administered prices in the drug industry, S. Rep. 448, 87th Cong., 1st Sess.

[21] Admin. Reps. at 927.

[22] Annual Report of the Federal Security Agency, Food and Drug Administration (1950) at 12.

[23] In 1961, Secretary of Health, Education, and Welfare Ribicoff testified before Congress on the need for efficacy data in NDAs, stating: "It is important to recognize that evaluating effectiveness is not a new concept in the administration of the food and drug law. In some instances the decision as to safety of a new drug necessarily requires an evaluation of effectiveness. If the drug is offered for treatment of progressive or life threatening diseases, such as cancer, or if the drug is seriously toxic or has alarming side effects, we now consider its effectiveness. In such cases, the determination of safety is, in the light of the purpose of the new drug provisions, inseparable from consideration of the drug's effectiveness." Hearings before the Subcommittee on Antitrust and Monopoly, Senate Committee on the Judiciary, 87th Cong., 1st Sess., on Drug Industry AntiTrust Act, Part 5, at 2588.

This was followed by the introduction of legislation to amend the 1938 Act.

On July 19, 1962, the Committee reported out a bill (S. 1552, 87th Cong.) designed to "keep unfit drugs off the market * * * and speed their removal should they reach the market." [24] A proposed amendment to Section 505 (21 U.S.C. (1958 ed.) 355) authorized suspension of an NDA "upon a finding that there is a lack of substantial evidence * * * that [the drug] will have the effect claimed for it." [25] But the bill did not alter the definition of "new drug," which remained a drug not generally recognized as safe.

At about the same time, reports of the thalidomide drug disaster startled the country.[26] On August 4, 1962, President Kennedy sent to the Chairman of the Senate Committee on the Judiciary a series of proposed amendments to the pending bill. These were introduced and explained on the floor of the Senate by Senator Kefauver (108 Cong. Rec. 15692–15698). They included, among other things, a proposal for affirmative administrative approval of NDAs in place of the existing procedure permitting applications to become automatically effective after a fixed time unless rejected; redefinition of "new drug" to include effectiveness, as well as safety; and a standard which would give meaningful content to the existing bill's

[24] S. Rep. No. 1744, Part 1, 87th Cong., 2d Sess., at 8.

[25] *Id.* at 16.

[26] Thalidomide, a tranquilizer which was extensively used in Europe with labeling asserting safety in treatment of pregnant women, resulted in teratogenic impairment to thousands of infants. See *id.* at 40–42.

undefined criterion for "substantial evidence" of effectiveness.

Because of the President's proposals and nationwide concern over the thalidomide tragedy, the Senate committee met again "to give further special consideration to the adequacy of the present provisions of the Food and Drug Act" from a safety and efficiency standpoint. On August 21, 1962, it issued a second part to its report, setting forth a substitute version of S. 1552 which was designed to "insure the reliability of drugs." [27]

The Committee reported four important changes relevant to these cases. First, the bill provided that "no new drug could go on the market without affirmative approval by the Department." [28] Second, it added effectiveness to the safety standard in the definition of "new drug." The Committee explained that "[t]he effect of this change is to require that all claims for effectiveness, whether made initially in a new-drug application or at any time thereafter, must be supported by 'substantial evidence'" as defined in the amendments, and that this change was being made in order "to eliminate any possible ambiguity" on this point.[29]

Third, it specifically defined "substantial evidence" in terms of adequate and well-controlled studies by experts, as distinguished from anecdotal evidence

[27] S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess., at 1.
[28] *Id.* at 4.
[29] *Id.* at 5.

by individual practitioners. The Committee explained that:[30]

> a claim could be rejected if it were found (a) that the investigations were not "adequate"; (b) that they were not "well controlled"; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which the application is made; or (d) that the conclusions drawn by such experts could not fairly and responsibly be derived from their investigations. * * *
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> * * * The question of whether the claim would or would not be allowed would be determined by [the Secretary's] evaluation of whether the claim had been supported by substantial evidence as defined above.

Fourth, the Committee proposed detailed transitional provisions, including a grandfather clause, for the new effectiveness standard. These provided that outstanding NDAs would be treated as approved under the new standard unless they were made the subject of further proceedings; that manufacturers would have a two-year grace period in which to gather substantial evidence of effectiveness; and that "in the case of a drug on the market which was never subject to the new-drug procedure before," the new effectiveness standard "would not apply to existing labeling claims."[31] Beyond making clear that drugs which had not been legally subject to the 1938 Act were not to be subject to the new amendments, there

[30] *Id.* at 6.
[31] *Id.* at 8.

was little other explanation of the grandfather provision.[32] Me-too drugs were not discussed during the debates when the bill passed the House and Senate. In conference, the Senate version of the grandfather provisions was adopted.[33] The bill finally enacted, save for certain additional amendments not here relevant, was substantially the revised bill proposed by the Senate Committee.

2. The Act as amended

For purposes of the present cases, the relevant substantive provisions of the 1962 Act (76 Stat. 780) are those dealing with efficacy and the definition of substantial evidence. As amended, Section 201(p)(1) now defines "new drug" as any drug not generally recognized among experts as safe *and effective* for its intended use. 21 U.S.C. 321(p)(1), J.A. 475. Section 505(a) bars the marketing of a new drug unless an approved application is in effect for it. 21 U.S.C. 355(a). Section 505(b) now requires an applicant to submit data demonstrating the safety *and efficacy* of the product involved. 21 U.S.C. 355(b), J.A. 477. The Secretary must either approve or disapprove the application within 180 days. Section 505(c), 21 U.S.C. 355(c). Section 505(d) requires the Secretary, after

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[32] Senator Eastland explained the Committee's revised bill on the floor of the Senate. Discussing the grandfather provision, he said: "Established drugs which have never been required to go through new drug procedures will not be affected by the new effectiveness test insofar as their existing claims are concerned." 108 Cong. Rec. 17366.

[33] H. Rep. 2526, 87th Cong., 2d Sess., at 22–23.

notice and opportunity for hearing, to refuse to approve the application if he finds a lack of "substantial evidence" of the product's efficacy. 21 U.S.C. 355(d), J.A. 478–479. Section 505(e)(3) now requires the Secretary to withdraw approval for an NDA, after notice and opportunity for hearing, if he finds upon the basis of new information a lack of "substantial evidence" of the drug's efficacy. 21 U.S.C. 355(e)(3), J.A. 479. Section 505(d) defines "substantial evidence" of effectiveness, as used in that subsection and in subsection (e), as "adequate and well-controlled investigations" from which qualified experts could conclude that the product is effective. Orders denying and withdrawing approvals are made directly reviewable in the courts of appeals. Section 505(h), 21 U.S.C. 355(h), J.A. 480–481.

Also relevant are the transitional and grandfather provisions. Since the Act was amended to require affirmative agency approval under the new standards, NDAs "effective" prior to the 1962 amendments were deemed "approved" under the new standards. This approval could not be withdrawn for lack of substantial evidence of effectiveness under Section 505(e)(3) for a period of two years. P.L. 87–781, 76 Stat. 788–789, Sections 107(c)(2) and 107(c)(3)(B), J.A. 481–482. The "grandfather" clause for the new efficacy provisions exempted any drug which, on the day preceding the enactment date (*i.e.,* October 9, 1962) was (A) sold in the United States, (B) generally recognized as safe, and (C) "not covered by an effective application under Section 505," so long

as its intended uses remained unchanged. P.L. 87-781, Section 107(c)(4), J.A. 482.

The injunctive, criminal, and seizure provisions of the 1938 Act remained essentially unchanged.

D. FDA'S IMPLEMENTATION OF THE 1962 AMENDMENTS

During the four years following enactment of the 1962 amendments, the agency concentrated on processing the large number of NDAs filed as a result of the new legislation. By 1966 the backlog was overcome, as the number of original NDAs received in that year dwindled to 147 [34] from a high in 1963 of 1,149.[35] The agency then took its first steps to review efficacy claims of drugs that had been cleared for marketing before 1962 on the basis of safety data only.

1. The NAS–NRC Drug Efficacy Study. To aid it in reviewing efficacy claims for every drug cleared for marketing before passage of the 1962 amendments, the FDA called upon the National Academy of Sciences-National Research Council (NAS-NRC).[36] This organization established a Drug Efficacy Study Group to determine whether there was appro-

[34] Annual Report of U.S. Department of Health, Education, and Welfare (1966), at 198.

[35] Annual Report of U.S. Department of Health, Education, and Welfare (1963), at 311.

[36] The National Academy of Sciences was created by Act of Congress in 1863 (12 Stat. 806). It is a non-governmental organization of scientists, whose duties include investigating and reporting upon scientific matters at the request of government departments. The NAS organized the National Research Council under its charter at President Wilson's request (see Executive Order 2859 (May 11, 1918), as amended by Executive Order 10668 (May 10, 1956), 21 Fed. Reg. 3155). The NRC is, in effect, the principal operating agency for the NAS.

priate scientific evidence to support the efficacy claims of those drugs. Thirty panels, each composed of six experts in a particular field of drug therapy, reviewed the manufacturer's claims and its evidence of efficacy for the drugs in their field of expertise (there were, for example, panels on drugs for relief of pain, anesthesiology, dermatology, ophthalmology, etc.).[37] To facilitate this review, manufacturers were ordered to submit to the appropriate panel or panels a special report containing the best available evidence in support of the efficacy claims for their drugs.[38] The report was to include identification of the drug, copies of its labeling, a bibliography of publications pertinent to the claims and any available unpublished data that the manufacturer wished to have considered. 31 Fed. Reg. 9426, 13014, J.A. 193–194, 288–289.

The panels based their conclusions upon factual information from scientific literature, from the Food and Drug Administration, and from the manufacturer or other sources, as well as upon the experience and informed judgment of the members of the panels.[39] Of the some 4,000 drug formulations still marketed by 237

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[37] Drug Efficacy Study: Final Report to the Commissioner of Food and Drugs, Food and Drug Administration, from the Division of Medical Sciences, National Research Council, National Academy of Sciences, Washington, D.C., 1969, at 1–3 (hereafter "NAS–NRC Report").

Ten copies of this Report have been furnished to the Clerk of this Court.

[38] Drugs involving claims falling within the scope of inquiry of more than one panel were reviewed by each panel with respect to the claim or aspect of a claim relevant to its inquiry. NAS–NRC Report, at 5.

[39] *Id.* at 42.

firms, the panels found a "considerable number" effective and about 7 percent ineffective or ineffective as fixed combinations for all claims; the majority received varying findings of "probably effective," "possibly effective," "effective but," and "effective" for some of the numerous claims made in each drug's labeling.[40] The Academy expressed concern over the quality of evidence available to support the efficacy claims of these drugs:[41]

> * * * Many of the presentations submitted by manufacturers in support of the claims made for the use of their drugs consisted of bulky files of reports of uncontrolled observations and testimonial-type endorsements. *The lack of substantial evidence based on well-controlled investigations by experienced investigators was conspicuous.* Moreover, searches of the medical literature indicated that there existed little convincing scientific evidence to support many of the cited indications for the use of drugs that are currently in good standing in medical practice. * * * [Emphasis added.]

Of some 16,500 claims made in the labeling of these drugs, only about 19 percent were found to be effective. The other claims, rated variously from "ineffective" to "effective but", were found not to be supported by substantial evidence of effectiveness.[42] Al-

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[40] *Id.* at 5, 7, 12.

[41] *Id.* at 13.

[42] See Hearings before the Subcommittee on Monopoly, Senate Select Committee on Small Business, 92d Cong., 1st Sess., on Present Status of Competition in the Pharmaceutical Industry, Part 20, at 7975. After allocation of "effective but" claims to other categories, about 30% of the claims were deemed effective (*id.* at 7976).

though the NAS–NRC panels reviewed more than 4,000 drugs for which NDAs were in effect, they did not specifically evaluate the still unknown larger number of me-too drugs.[43]

2. *Implementation of the NAS–NRC study.* On January 23, 1968, FDA held a government-industry conference and announced its policy of applying to all drugs, including "me-too" drugs, the applicable NAS–NRC efficacy findings.[44]

The agency believed that it would be inconsistent and unjust to drug manufacturers and to the public to construe the Act as requiring manufacturers of the "pioneer" drugs, who had filed an NDA, to produce substantial evidence of effectiveness or lose their marketing approval, while at the same time permitting "me-too" drugs, which owed their marketability to the pioneer NDAs, to remain on the market without demonstrating effectiveness. Construing the 1962 amendments as a mandate to assure that *all* pre-1962 drugs be shown effective as well as safe, the agency interpreted the words "covered by an effective application" in the 1962 grandfather clause (Section 107(c)(4)(C)) to refer "generically" to all of the types of drugs for

[43] Hearings before the Senate Committee on Labor and Public Welfare, on Drug Listing Act, 1971, 92d Cong., 1st Sess., at 21–22.

[44] *FDA Papers*, March 1968, at 15–16. This publication is the official magazine of the FDA, published monthly. It contains, *inter alia*, the notices of judgments, decrees, and court orders required to be published under Section 705 of the Act, 21 U.S.C. 375, as well as other information authorized to be published by that provision. Two copies of the March 1968 edition are being lodged with the Clerk of this Court.

which at least one NDA had become effective. Its interpretation precluded "grandfather" protection for all pre-1962 drugs identical, similar or related to those for which an NDA was permitted to become effective. Accordingly, participants at the January 1968 conference were told that the NAS–NRC findings would be applied not only to "drugs which were specifically the subject of prior new-drug approvals but also any 'me-too' drugs * * *." [45]

The participants were also advised that the very first notice proposing withdrawal proceedings to implement the NAS–NRC findings (covering bioflavonoid products [46]) would be a model for future actions insofar as it would "classify all drugs containing any [ineffective] components as new drugs for which an approval is not in effect." [47]

Plans to classify those drugs generally recognized as safe and effective for labeled indications were also disclosed at that conference,[48] as well as the agency's policy to require manufacturers to file either full, abbreviated, or supplemental NDAs for changes in labeling or drug composition determined to be necessary by the NAS–NRC findings.[49]

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[45] *Ibid.*

[46] 33 Fed. Reg. 818 (J.A. 290). These are the products involved in *USV Pharmaceutical* (No. 72–666).

[47] *FDA Papers*, March 1968, at 16.

[48] *Id.* at 10.

[49] *Id.* at 11. A complete NDA is required for an unapproved "new drug." 21 C.F.R. 130.4. Supplemental applications are required for a change in either the labeling or composition of an NDA'd drug. 21 C.F.R. 130.9. In the case of a "new drug"

On May 28, 1968, the agency, by formal statement of policy premised on the need for full implementation of the NAS–NRC findings, revoked all opinions previously given to the effect that an article is "no longer a new drug."[50] On July 10, 1968, the first notice of opportunity for hearing on a proposal to withdraw NDA approvals was published.[51] Other proposals followed, and approximately 600 have been issued to date.

FDA has recently adopted a regulation declaring the manner in which Drug Efficacy Study Implementation ("DESI") Notices and Notices of Opportunity for Hearing apply to identical, related, and similar drugs. It defines an "identical, related, or similar drug" to include "other brands, potencies, dosage forms, salts, and esters of the same drug moiety as well as of any drug moiety related in chemical structure or known pharmacological properties."[52] It also provides all persons with an interest in such drugs an opportunity for hearing on any proposed withdrawal of NDA approval for the basic drug.[53]

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shown in connection with a previous NDA approval to be safe and effective, a manufacturer of the same or a similar drug not having an NDA may file an abbreviated application containing the information required by 21 U.S.C. 355(b), except safety and efficacy data. In certain instances, therapeutic equivalency must be demonstrated. 21 C.F.R. 130.4(f).

[50] 33 Fed. Reg. 7758; 21 C.F.R. 130.39 (J.A. 291–292).

[51] 33 Fed. Reg. 9908 (J.A. 293).

[52] 37 Fed. Reg. 23185, adding Section 130.40 to 21 C.F.R.

[53] In *American Public Health Association* v. *Veneman*, Civil No. 1847–70 (D.D.C.), a district court ordered the agency to

3. *Regulations defining "adequate and well-controlled investigations" and requiring proffer of evidence conforming to that definition as a basis for hearing.* As a result of the NAS–NRC study and its implementation by notices proposing to withdraw approvals on drugs found to be lacking substantial evidence of effectiveness, the agency was faced with the prospect of more than 1,000 withdrawal hearings under Section 505(e), each lasting several months.[54] This would have delayed for many years achievement of the purposes of the 1962 amendments. The agency therefore issued regulations in 1969 defining the "scientific principles which characterize an adequate and well-controlled clinical investigation,"[55] the standard for "substantial evidence" in Section 505. The rule also provided that, unless a party seeking a hearing was prepared to proffer such evidence, no basis for a hearing was presented.[56] Following re-promulgation of these regulations in May 1970 to comply with the rule-making provisions of the Administrative Pro-

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apply the NAS–NRC evaluation to all me-too drugs (see paragraph XI of the order). The order is reproduced at 37 Fed. Reg. 26623–26624.

[54] Of the drugs reviewed by NAS–NRC, more than 3,500 made one or more claims not rated effective, and withdrawal of approval is in prospect for most of these claims. In many instances, however, several products contain similar drugs, so that consideration of withdrawal of approval for similar claims can be undertaken with respect to several products in a single, consolidated proceeding. Thus, the precise number of such proceedings is impossible to estimate.

[55] 34 Fed. Reg. 14596.

[56] *Id.*

cedure Act,[57] they were sustained on judicial review.[58]

4. The Drug Listing Act of 1972. By May 1972, 102 final orders effecting withdrawal of approval for 452 NDAs had been published. These orders also resulted in removal from the market of an additional 1,473 related or "me-too" drugs.[59] However, FDA still had no assurance that its implementation efforts were broadly effective, for a census of the marketplace was not authorized by the statute.

On August 16, 1972, in an effort to provide the agency with the tools necessary to effectuate the findings of the NAS–NRC review, Congress enacted the Drug Listing Act of 1972, P.L. 92–387, 86 Stat. 559. It requires manufacturers to submit to the agency a list of all drug products they market, including data showing the composition of the drugs, their labeling and advertising. The Senate report explained the necessity for this legislation.[60]

> The effective enforcement of the drug provisions of the Act requires the ready availability of a current inventory of all marketed drugs.

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[57] 35 Fed. Reg. 3073; 35 Fed. Reg. 7250. The regulations had been set aside in *Pharmaceutical Manufacturers Association* v. *Finch*, 307 F. Supp. 858 (D. Del.), for failure to give the public an opportunity to comment upon them. In a suit by a manufacturer which had actual notice of the procedures, however, a court of appeals held that the agency's definition of "substantial evidence" complied with the intent of Congress. *Upjohn Co.* v. *Finch*, 422 F. 2d 944 (C.A. 6).

[58] *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del.).

[59] Hearings on the Present Status of Competition in the Pharmaceutical Industry before the Subcommittee on Monopoly of the Senate Select Committee on Small Business, 92d Cong., 2d Sess., Part 22, at 8525.

[60] S. Rep. No. 92–924, 92d Cong., 2d Sess., at 2.

> The Secretary is just completing a thorough review of the effectiveness of drugs marketed pursuant to new drug applications during the period 1938–1962, as required by the Drug Amendments of 1962. Application of the results of this important review to related drugs would be frustrated if a list of all marketed drugs were not easily obtained. * * *

The first filing of the drug lists by the industry will take place during June 1973. 37 Fed. Reg. 26432.

5. Regulations Pertaining to Over-the-Counter Drugs. FDA has also recently concluded that it is impossible for it to apply the Drug Amendments of 1962 effectively to over-the-counter (OTC) drugs on a case-by-case basis. There are estimated to be between 100,000 and 500,000 of these products, few of which were previously approved under the Act and many of which are of questionable efficacy. FDA does not have the resources to proceed against these products individually, and the time consumed by litigation would deny the public protection for many years to come. 37 Fed. Reg. 85–86. It therefore proposed (*id.*) and, in May 1972, adopted (37 Fed. Reg. 9464) a procedure for determining in substantive rule making, by therapeutic class, whether particular OTC products not covered by NDAs are generally recognized as safe and effective and not misbranded, under the standards of the Act. The procedure involves the establishment of independent expert panels for different categories of OTC drugs (*e.g.*, antacids, laxatives, analgesics), which would review all available data (including any that manufacturers, consumer groups, or others wish to submit) and prepare monographs prescribing drug

composition, labeling, and manufacturing controls. Products conforming to the monograph-rule will not be considered to be "new drugs" requiring an NDA or to be misbranded. The regulation contemplates substantial procedural safeguards at the administrative level (a hearing before the expert panel, comments and rebuttal comments on the proposed monograph-rule, and objections to and hearing before the Commissioner on the tentative final monograph-rule) and judicial review of the monograph-rule, which could thereafter be enforced in the courts as binding (37 Fed. Reg. 9464, 9475).

II. THE FIVE CASES CONSOLIDATED IN THIS COURT

The five consolidated cases relate to numerous important aspects, both substantive and procedural, of FDA's efforts to accomplish the purposes of the 1962 efficacy amendments as applied to drugs that came on the market prior to 1962. *USV Pharmaceutical* (No. 72–666) and the cross-petition in *Hynson, Westcott and Dunning* (No. 72–414) pose questions as to which classes of drugs marketed prior to 1962 are subject to the Act's requirement of proof of efficacy for continued marketing. They involve principally the construction of the transitional and grandfather provisions of Section 107(c). The government's petition in *Hynson, Westcott and Dunning* (No. 72–394) concerns the validity and application of FDA's procedural regulations requiring a manufacturer of a drug to support its request for an evidentiary hearing in a withdrawal proceeding with a showing that it can adduce the kind of evidence required by statute to establish the efficacy

of the drug. *CIBA* (No. 72–528), the cross-petition in *Hynson, Westcott and Dunning* (No. 72–414), and the present case raise the question, in varying contexts, whether FDA has authority to decide initially in an administrative proceeding whether a product is subject to the proof-of-efficacy provisions of the Act. In *CIBA* and *Hynson, Westcott and Dunning* the question arises in the context of an agency proceeding to withdraw marketing approval previously obtained by the manufacturer. In the present case, the question is whether FDA may decide that issue pursuant to a referral from a district court.

III. THE INSTANT CASE

Administrative Proceedings. Prior to 1962, under the safety standard of the 1938 Act, FDA had permitted NDAs covering pentylenetetrazol combination drugs [61] to become effective. The NDAs were held by firms not involved in the present case. As part of the comprehensive DESI program (see pp. 19–21, *supra*), three separate NAS–NRC panels reviewed the available evidence concerning these drugs (J.A. 235–247).[62] Each panel concluded that the drug was "ineffective"

[61] These are prescription drugs offered for senile psychosis and psychoneurosis, with anxiety and nervous tension, senile fatigue, confusion, debilitation, depression, dizzy spells, mild behavioral disorders, irritability and functional memory defects (J.A. 233).

[62] The specific drugs evaluated were NICOZOL with RESERPINE (a combination of pentylenetetrazol, nicotinic acid and reserpine) and GERONIAZOL injection (a combination of pentylenetetrazol and nicotinic acid administered by injection) (J.A. 235, 240–241).

for each of its indicated uses (J.A. 237, 239, 244, 245, 247).

After evaluating the NAS–NRC reports on drug combinations containing pentylenetetrazol, the Commissioner concluded that there was a lack of substantial evidence that these drugs are effective for their intended uses. On August 26, 1969, he published a notice (34 Fed. Reg. 13673, J.A. 226–228) setting forth his conclusion and announcing his intention to initiate proceedings to withdraw approval of the NDAs for these drugs. The notice invited the holders of the NDAs "and any interested person who might be adversely affected by [the drugs'] removal from the market" to submit any "adequate and well-controlled studies bearing on the efficacy of" the drugs in question. The notice reflected FDA's view that withdrawal of approval of the NDAs would operate to remove marketing approval not only for the particular drugs expressly covered by the NDAs, but also for any drugs of similar composition. It stated that an order withdrawing approval of the NDAs "will cause any such drug on the market to be a new drug for which an approved new-drug application is not in effect and will make it subject to regulatory action."

Only one firm, a holder of one of the three NDAs outstanding, submitted further material in response to the notice. On May 20, 1970, the Commissioner announced that substantial evidence of effectiveness within the meaning of the statute (21 U.S.C. 355(d)), was lacking and that he therefore proposed to issue an order under Section 505(e) of the Act (21 U.S.C. 355

(e)) withdrawing approval of the NDAs. The three firms that held approved NDAs "and any interested person who would be adversely affected" by such action were again offered an opportunity for a hearing. The agency also again declared that withdrawal of approval for the NDAs would cause any drug containing the same substances to be a "new drug" for which an approved NDA is not in effect (35 Fed. Reg. 7749, J.A. 228–230). Only one NDA holder requested a hearing, but it filed no data to support its request. Accordingly, the Commissioner issued orders withdrawing approval for the three NDAs then in effect (35 Fed. Reg. 14412, J.A. 231, 232). No appeal was taken to review this action.

The NAS–NRC efficacy review of drugs containing pentylenetetrazol and the ensuing agency proceedings that culminated in the order withdrawing approval of the NDAs would have offered little protection to the public if others continued to market identical or substantially similar drugs ("me-too" drugs). Accordingly, the agency issued advisory letters to various firms intended to effect the removal from the market of all "me-too" drugs containing pentylenetetrazol. For example, on November 4, 1970, FDA wrote Bentex Pharmaceuticals advising it of FDA's action withdrawing approval for NDAs on drugs similar to Bentex products containing pentylenetetrazol and stating that, in view of this, those Bentex products were no longer marketable (J.A. 254, n. 3).

The Decision of the District Court. On December 1, 1970, Bentex and 22 other firms [43] that market drugs containing pentylenetetrazol filed this suit for declaratory and injunctive relief (J.A. 219–226). They contended that their drugs containing pentylenetetrazol either (1) are not "new drugs" within the meaning of Section 201(p)(1) of the amended Act (21 USC 321(p)(1)) (*i.e.*, that they are currently generally recognized as safe and effective) or (2) are exempted by the grandfather clause from the requirements of the amended Act (J.A. 223).[44] They accordingly sought a ruling declaring invalid and unenforceable the Commissioner's position that their drugs are "new drugs" for which no NDA is in effect and which therefore cannot legally be marketed.

The district court held that the declaratory judgment action was properly before it and that it could determine whether plaintiffs' drugs required approved NDAs in order to be lawfully marketed—*i.e.*, whether or not they are "new drugs" or "grandfathered" drugs (J.A. 256). It thus rejected the government's conten-

[43] A twenty-fourth firm, O'Neal, Jones & Feldman, Inc., which alleged that it contemplated the sale of drugs containing pentylenetetrazol (J.A. 220), was stricken as a plaintiff in this case at its request.

[44] The complaint asserted that the drugs involved were protected by the grandfather clause of the 1938 Act, set forth in Section 201(p)(1), which applies to drugs marketed before 1938 (J.A. 223). It later became clear that plaintiffs were actually relying on the grandfather provision in Section 107(c)(4) of the 1962 amendments.

tion that FDA has primary and exclusive jurisdiction to determine that issue (J.A. 255). But the district court also rejected the argument, advanced by plaintiffs, that the status of their drugs could be determined only by the district court. It ruled that the statutory "grant of authority to approve or withhold approval of new drug application [*sic*], or to proceed with regulatory action in the courts, necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which requires an approved new drug application for lawful interstate shipment" (*ibid.*).

Having found concurrent jurisdiction, the district court concluded that FDA, as "the more able arbiter of the question," should resolve the "new drug" issue in an administrative proceeding in which plaintiffs and other interested parties could participate (J.A. 256).[65] The court entered an injunction to preserve the *status quo*, barring enforcement proceedings against the drugs involved pending resolution by FDA of the question whether they require approved NDAs in order to be lawfully marketed. If the agency should decline to hold a hearing and decide the issue, the court stated it would then determine the issue itself (J.A. 257–258).

The Decision of the Court of Appeals. On appeal by the plaintiff drug manufacturers,[66] the court of

[65] The district court stated that an appeal from FDA's determination would lie to the court of appeals (J.A. 256). We believe, however, that FDA's determination in response to the court's referral order would be reviewable in the district court. See *infra*, pp. 52–53.

[66] The government did not appeal.

appeals reversed and remanded the case to the district court with directions that it determine whether plaintiffs' drugs may lawfully be marketed without approved NDAs (J.A. 258–270).[67]

The court of appeals held that the Act confers no jurisdiction on FDA, either primary or concurrent, to decide in an administrative proceeding whether a product is a "new drug" for which an NDA is required. There is thus no basis, it concluded, for referring the issue to the agency, because the agency has no authority to decide it (J.A. 266). The court based this conclusion on its construction of the Act as "establish[ing] two forums for the regulation of drugs: One is administrative and deals with the procedures for securing pre-marketing clearances for the statutorily defined 'new drug', with right of appeal from a denial of approval, or withdrawal of a previous approval * * *; the other is judicial and is intended to make effective and give strength to the requirement that 'new drugs' be cleared as safe [and, after 1962, effective] before marketing by providing the Government with certain potent judicial remedies [seizure, injunction and criminal prosecution], *available exclu-*

[67] The court of appeals expressed the view that the only substantive issue in the case is whether respondents' drugs are exempt from the proof of efficacy requirement of the amended Act by reason of the grandfather provision, Section 107(c)(4), and it directed the district court to determine that issue on remand (see J.A. 263, 269). So far as we are aware, however, respondents have not abandoned their claim that their drugs are not "new drugs" within the meaning of Section 201(p)(1), *i.e.*, that they are now generally recognized as safe and effective.

sively in the District Court" (J.A. 260; emphasis in original).

The court stated that since there is no express provision in the Act for an administrative determination of whether a particular drug is a "new drug" requiring an NDA, and no provision for judicial review of such a determination (J.A. 259, 267–268), the manufacturer, "who must act at its peril," must decide whether an NDA is required for the lawful marketing of a particular drug (J.A. 260, 268). In the court of appeals' view, the correctness of the manufacturer's determination must be decided exclusively by the district court, either in an action initiated by the government or in an anticipatory declaratory judgment action like this one, if the agency has made known its "prosecutorial" views (J.A. 266–267, 269).

The court of appeals expressly rejected the district court's reasoning that the statutory grant of authority to FDA to approve or withhold approval of NDAs necessarily implies authority to resolve the threshold question whether an approved NDA is required. "No such issue," the court of appeals said, "is posed by the application" (J.A. 268). Rather, the filing of the application represents a "concession" by the manufacturer that its drug is a "new drug" requiring administrative approval. The sole question raised by an application is whether the drug is safe and effective, and the agency may determine only that issue when an application is filed (*ibid.*). The court held that if the manufacturer chooses not to make that concession, but rather to market at its peril, the courts provide

the only forum within which the legality of that choice may be determined.

The court of appeals remanded the case to the district court for determination of the substantive issues involved (J.A. 269–270).

ARGUMENT

INTRODUCTION AND SUMMARY

The court of appeals has ruled that FDA lacks power, in all circumstances, to determine whether particular drugs require an approved NDA in order to be sold to the public.[68] Although Congress assigned the agency primary responsibility for determining whether drugs proposed for sale, or now being sold, are safe and effective for their intended use, the decision below nevertheless holds that FDA cannot determine the threshold question whether particular products are "new drugs" subject to its jurisdiction under Section 201(p) of the Act. It follows, under this rea-

[68] That the court below considered its ruling to bar administrative determination of the Act's coverage in any circumstances is demonstrated by its rulings in two of the related cases pending in this Court. In *Hynson, Westcott and Dunning*, No. 72–394, a petition for review of the agency's order withdrawing NDAs, the court held that a manufacturer is entitled to have the district court resolve its claim for exemption, under the grandfather clause of the 1962 amendments, from the new efficacy requirements (J.A. 176–177). And in *USV Pharmaceutical*, No. 72–666, an appeal by the government from a district court judgment declaring a manufacturer's products exempt under the grandfather clause, the court of appeals, citing its decision in the instant case, ruled that the district court alone had jurisdiction to determine these questions (J.A. 467).

soning, that it cannot determine whether such products are exempted from the efficacy requirements of the Drug Amendments Act of 1962 by the grandfather clause in Section 107(c)(4) of that Act. If the court of appeals is correct, only the courts may make these determinations, even though the agency's jurisdiction depends on them.

This decision strikes at the heart of the statutory scheme for administrative examination of drugs for safety and effectiveness. That scheme contemplates that before drugs are marketed they will be examined by an expert agency in the light of the best scientific information available, and that they will thereafter be reexamined in the light of developing knowledge whenever this is necessary to protect the public. But the decision below would, in all instances, effectively transfer to the courts resolution of the complex medical and pharmacological questions upon which the definition of "new drug" turns. An enormous volume of case-by-case litigation would thus be thrust upon district courts, whose dockets are already crowded. Moreover, the courts are not equipped with expert scientific staffs to investigate and resolve the technical questions presented, nor do they have the broad range of administrative powers, including rule-making, by which the agency can create procedures to reduce to manageable proportions the enormous numbers of products and claims which must be examined. See, *e.g., Abbott Laboratories* v. *Gardner,* 387 U.S. 136, 147, 149–150, 151–152; *Securities and Exchange Commission* v. *Chenery Corp.,* 332 U.S. 194, 202; *Ciba-Geigy Corporation* v. *Richardson,* 446 F. 2d 466, 467-

468 (C.A. 2); *American Airlines, Inc.* v. *Civil Aeronautics Board*, 359 F. 2d 624, 629–630 (C.A.D.C.), certiorari denied, 385 U.S. 843.

The holding of the court of appeals is directly inconsistent with the established principle that administrative agencies having regulatory responsibilities with respect to particular industries, in the absence of conflict with other statutory schemes,[69] have primary authority to determine the coverage of the Act they administer. It is also inconsistent with principles governing the discretion of district courts in declaratory judgment actions. And it threatens virtually to paralyze achievement of the basic objective of the 1962 amendments—removal from the market of *all* unsafe and ineffective drugs.

As a practical matter, the agency cannot proceed entirely on a case-by-case, drug-by-drug, and claim-by-claim basis against every drug currently marketed or to be marketed that does not meet the standards of the 1962 amendments. Nor, we submit, are the federal courts equipped to handle a flood of complex scientific litigation. Under the court of appeals' rationale, however, in every instance in which an NDA is withdrawn by the agency after full administrative proceedings, and even after that decision is sustained in the court of appeals on petition for review, the manufacturer would have the right to litigate afresh in a district court the question whether the drug involved required an NDA in the first place.

[69] Cf. *Ricci* v. *Chicago Mercantile Exchange*, No. 71–858, decided January 9, 1973.

Moreover, the decision invites manufacturers of "me-too" drugs to refrain from participating in agency proceedings for the withdrawal of approval for the primary NDA, in order to litigate in the district courts the question whether their drugs require approved NDAs to remain on the market. The court below thus encourages, indeed mandates, a two-step proceeding: first, a full scale administrative proceeding denying or withdrawing approval under Section 505; then a separate series of judicial proceedings to establish whether the Act's requirements should be applied at all. If permitted to stand, the court of appeals' holding therefore would, at a minimum, inordinately protract FDA's efforts to discharge its congressionally assigned responsibility to remove from the market drugs not shown to be effective.

By contrast, the district court's decision, referring issues of the Act's coverage to the agency responsible for administering it, would encourage manufacturers, whether producers of NDA's or "me-too" drugs, to look to FDA in the first instance to determine the applicability of the Act to their products.[70]

Moreover, the implications of the decision below extend beyond the area of prescription drugs involved

[70] In the government's view, a drug found to be a "me-too" drug would have been "covered by" an effective NDA at the time of the 1962 amendments and would therefore not be within the grandfather provision of Section 107(c)(4). This issue is involved in *USV Pharmaceutical* (No. 72-666). If FDA's position is sustained, the "me-too" manufacturers will have a compelling incentive to participate in proceedings to determine whether approval of the primary NDA should be withdrawn for lack of efficacy of the drug involved.

in the present case. The agency's current program to review the over-the-counter drugs (see pp. 24–25, *supra*) would also be undermined by the court of appeals' rationale, since the agency would have no power to determine definitively, subject to judicial review, standards by which hundreds of thousands of drugs for which no NDA is in effect may be classified as "new drugs" or not. The agency would be required to pursue these products throughout the courts of the Nation in innumerable trials considering *de novo* issues that are best suited to administrative resolution and that may, indeed, already have been given careful consideration in administrative proceedings. The decision of the court of appeals would thus leave the agency virtually impotent to deal effectively with the vast task of implementing the 1962 amendments.[71]

Nothing in the Act requires results so crippling to its effective implementation. Congress assigned to the agency a responsibility affecting the lives and health of all Americans—to assure that drugs sold in the United States are safe and effective. This responsibility carries with it the grant of a commensurately wide range of express and implicit powers neces-

[71] The implications of the decision below extend beyond drugs and would apparently also affect the agency's authority to determine administratively whether food ingredients are generally recognized as safe under 21 U.S.C. 348 (see 37 Fed. Reg. 25705) or are grandfathered under 21 U.S.C. 321(s)(4) (see 37 Fed. Reg. 16407), to determine whether biologic substances licensed under 42 U.S.C. 262 are generally recognized as safe and effective (see 38 Fed. Reg. 4319), and to determine whether *in vitro* diagnostic products are safe and effective (see 37 Fed. Reg. 16613).

sary for achievement of the Act's ultimate purposes. Fundamental among these is the power to decide the threshold questions on which the agency's jurisdiction turns. This is clear from the structure of the Act itself, which places primary reliance on administrative pre-marketing clearance as the means of assuring that drugs sold to the American public are safe and effective for their recommended uses. The judicial remedies of injunction, condemnation, and criminal sanctions serve as a second line of defense, principally intended to channel maufacturers to the agency in the first instance.

The decision of the court of appeals that FDA has no jurisdiction to determine whether a product or class of products is a "new drug" requiring administrative pre-marketing clearance is rooted in several erroneous premises. Thus, contrary to the court's belief, there are procedural avenues available for consideration of the question by the agency, either in connection with the statutory proceeding for approval or withdrawal of an NDA (as in the companion *CIBA* case), or, if no NDA exists or is being sought, in a declaratory order proceeding pursuant to the Administrative Procedure Act. In either case, contrary to the assumption of the court below, judicial review of the agency's determination would be available—in the former instance, in the court of appeals by means of the Act's judicial review provision for actions affecting NDAs; in the latter, in the district courts pursuant to 28 U.S.C. 1331 and 1337 and the Administra-

tive Procedure Act's general provisions concerning review of final agency actions.

Finally, the court of appeals' assumption that there is a significant difference between the inquiry presented by the question of "new drug" status and that involved in the agency's review of NDAs for safety and efficacy is mistaken. Both inquiries focus upon expert evaluation of complex scientific data, and the substantial overlap in the content of the inquiries reinforces the conclusion that both were intended to be committed, wherever feasible, to the expert agency established by Congress to pass upon drug safety and efficacy.

Once the agency's jurisdiction to pass upon the questions referred to it by the district court in this case is recognized, the wisdom of the referral is apparent. The factual questions presented in this case—whether respondents' products are sufficiently similar to those for which NDAs were withdrawn for inefficacy to be "covered" by those NDAs; whether there exists substantial evidence of the effectiveness of respondents' products or general recognition, at any relevant time, of their safety or efficacy—turn upon the state of expert scientific opinion and upon complex chemical and pharmacological matters. Such matters are far better suited to initial determination by FDA rather than by a district court, and the referral to the agency in the instant case represented a sound exercise of the extensive equitable discretion vested in the courts in declaratory judgment proceedings.

I. FDA HAS AUTHORITY TO DECIDE WHETHER PARTICULAR DRUGS REQUIRE AN APPROVED NDA

A. THE SCHEME OF THE ACT CONTEMPLATES THAT AN EXPERT AGENCY WILL RESOLVE THE MEDICAL, CHEMICAL AND PHARMACOLOGICAL ISSUES INVOLVED IN DETERMINING "NEW DRUG" STATUS.

In concluding that the district court could not refer to FDA the question whether respondents' products are "new drugs" which require an NDA, the court of appeals held that the agency may never decide that question in its administrative capacity but may consider it only for the limited purpose of initiating enforcement proceedings in the courts. This holding, in our view, is based on an unduly narrow and mechanical reading of Section 505 of the Act which ignores the remedial purposes of the 1962 amendments and the over-all context of the Act, including the availability of proceedings authorized by the Administrative Procedure Act (see pp. 49–50, *infra*). It also misconceives FDA's administrative and prosecutorial functions. The former are intended to protect the public by providing pre-marketing administrative clearance and continuing post-marketing review for drugs in commerce. The latter, operating as a second line of defense, complement the agency's administrative functions by invoking judicial sanctions against those who fail to comply with the Act's regulatory requirements. This structure is apparent on the face of the Act.

1. The administrative provisions are the primary public safeguard. Section 505(a) of the Act (J.A. 477) expressly forbids introduction into commerce of "any

new drug, unless an approval of an application filed pursuant to subsection (b) of this section is effective with respect to such drug." Subsection (b) sets forth the requirements for filing an application with the Secretary of Health, Education and Welfare (*i.e.*, the Food and Drug Administration), and subsections (c) and (d) describe conditions for approval, with or without hearing, and grounds on which the agency may refuse an application. Subsection (d) includes the definition of "substantial evidence," which the manufacturer must present to support claims of the drug's effectiveness: "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have * * *" (J.A. 478). This is followed by subsection (e), which, recognizing that new research and clinical experience constantly change medical standards, contemplates that the agency will maintain a continuous surveillance of all previous approvals. Thus, the agency may withdraw previous approvals on the basis of new evidence that a product is unsafe or new information indicating that there is "a lack of substantial evidence" that the drug is effective (J.A. 479).

The statute thus contemplates a sweeping and comprehensive administrative responsibility, of a continuing nature, (1) to protect the public by screening

any "new drug" for safety and effectiveness prior to marketing, and (2) to maintain continuing surveillance of "new drugs" on the market in order to assure, in the light of developing medical knowledge and experience, that they are safe and effective for their intended use.

The broad powers of the agency to grant, refuse, or withdraw approvals are implemented by similarly broad powers to conduct hearings after due notice to the applicant (Section 505(c)(2), J.A. 477–478), "to promulgate regulations for the efficient enforcement of this Act" (Section 701(a), 21 U.S.C. 371(a)) and "to conduct examinations and investigations for the purposes of this Act" (Section 702(a), 21 U.S.C. 372 (a)).[12] Finally, any order of the agency refusing or withdrawing approval of an application may be appealed directly to the courts of appeals for review on the administrative record (Section 505(h), J.A. 480–481), so that the agency's exercise of its broad responsibilities is subject to the limited but important judicial scrutiny characteristic of American administrative law.

Congress has thus assigned the agency great responsibilities for the public health and conferred on it the full range of administrative powers to carry out these responsibilities: investigation, rule-making and administrative adjudication. There is every reason to construe this broad authority as including the power to decide the threshold question on which the agency's

[12] These powers, of course, extend beyond the drug provisions of the Act to the agency's responsibility for food, cosmetics, and other matters as well.

regulatory responsibility turns: Is the product involved a "new drug" for which approval is necessary under Section 505(a)?

"New drug" is a jurisdictional term of art in the statute. It is defined in Section 201(p) (J.A. 475) as "[a]ny drug * * * the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof * * *." The very statement of this definition, which must also be read in *pari materia* with the definition of substantial evidence in Section 505(d),[73] suggests a determination of technical and scientific questions by experts. It is thus an example of the classic administrative function—the resolution of technical issues of fact, requiring highly specialized knowledge, training and experience of a kind not ordinarily possessed by judges. See *Ricci* v. *Chicago Mercantile Exchange, supra; United States* v. *Western Pacific R. Co.*, 352 U.S. 59, 64–65, 65–66; *Far East Conference* v. *United States*, 342 U.S. 570, 574–575.

2. *The enforcement provisions complement the regulatory requirements.* When the enforcement provisions of the Act are read in relation to its regulatory provisions, it plainly appears that judicial proceedings are intended to complement, not displace, the regu-

[73] See S. Rep. 1744, Part 2, 87th Cong., 2d Sess., pp. 1, 5. See p. 41, *supra*.

latory scheme. The statute expressly lists, among other prohibited conduct, the introduction into commerce of any article in violation of Section 505's requirement of an NDA approved by the agency after administrative consideration. Section 301(d), J.A. 475. It prescribes civil injunction proceedings, criminal penalties, and *in rem* seizure and condemnation, to give effect to this as well as other prohibitions. Sections 302(a), 303, 304 (J.A. 475–477). The administrative system of pre-marketing clearance and continuing review is thus established by the Act as the primary means of safeguarding the public health from unsafe and ineffective drugs, while judicial sanctions reinforce the administrative agency as a second line of defense, hopefully functioning primarily to direct manufacturers to the agency in the first instance.

The court of appeals' decision, however, seriously departs from this system of administrative clearance supported by judicial review and sanctions. It would make the courts, not the agency, the principal forum for determining whether products are "new drugs" subject to the requirement of administrative clearance and review. Given the scientific and technical nature of the questions involved in these determinations, this would be an unusual policy choice for Congress, and, we submit, the language and structure of the Act do not require this unfortunate and impractical result.

The court of appeals considered it highly significant that there is "no provision in the Act for an administrative proceeding before the Secretary to compel the

filing of a 'new drug' application or to halt the marketing of a drug for which there is no approval by the Secretary" (J.A. 266). But this does not mean that, in the proceedings it does conduct, the agency is without power to determine its own jurisdiction. Sections 301 (d) and 505(a) together impose on manufacturers a duty to assure that their "new drugs" are covered by an approved NDA. The absence of administrative power to enforce this duty directly does not negate the agency's authority to make determinations with respect thereto. This Court so held in *Abbott Laboratories* v. *Gardner*, 387 U.S. 136, 151–152, where it rejected the government's argument that FDA's lack of administrative authority to enforce its regulations distinguished it from agencies having such power. Such administrative authority may be a useful remedial supplement to the judicial sanction, but it does not define the agency's substantive powers to resolve properly presented jurisdictional questions turning on technical matters peculiarly within the agency's competence.

Nor is it significant that in an enforcement proceeding the courts may determine for themselves whether a product is a "new drug," at least when the agency has not previously done so by formal administrative action.[14] For enforcement proceedings, which

[14] Where the agency has determined a question in formal administrative proceedings, subject to judicial review, a party to those proceedings may not, in the ordinary course, collaterally challenge that determination as a defense to an enforcement proceeding. See, *e.g.*, *United States* v. *Ruzicka*, 329 U.S. 287; *Yakus* v. *United States*, 321 U.S. 414, 444–446. This is

are brought in the name of the United States, are simply the last resort—the threat of judicial sanctions against those who disregard the administrative process. Such sanctions against operations without a permit required by statute are a familiar feature of the administrative process.[75] Indeed, even in an enforcement proceeding brought by the United States under a regulatory statute, technical questions under the statute within the primary jurisdiction of an agency may be referred to it. For example, in *United States* v. *Pacific & Arctic Navigation Co.*, 228 U.S. 87, a prosecution to enforce the antitrust laws and the Interstate Commerce Act, claims under the latter statute were referred to the Interstate Commerce Commission.[76] Similarly, under the scheme of the present Act,

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merely an application of the principle of collateral estoppel to interrelated administrative and judicial proceedings. Cf. *United States* v. *Utah Constr. Co.*, 384 U.S. 394, 422; *Marine Terminal Assn.* v. *Rederi. Transatlantic*, 400 U.S. 62, 72. See also 5 U.S.C. 703.

[75] See, *e.g.*, Sections 206(a) and 222(a) and (b) of the Motor Carrier Act, 49 U.S.C. 306(a), 322(a) and (b); Sections 401 and 902 of the Federal Aviation Act, 49 U.S.C. 1371 and 1472; Sections 301 and 501 of the Communications Act of 1934, 47 U.S.C. 301 and 501.

[76] In the present case, the government argued in the district court that FDA had primary jurisdiction and that the declaratory judgment action should be dismissed. Cf. *Far East Conference* v. *United States*, 342 U.S. 570, 576–577. But after the district court had ruled that it had concurrent jurisdiction, thereby rejecting the primary jurisdiction contention, it nevertheless referred the "new drug" question to the agency in the exercise of its equitable discretion. For purposes of this case, the government acquiesced in that determination and did not raise the primary jurisdiction argument on appeal. Consequently, it is not presented in this Court. The agency believes,

we submit that the courts serve as "collaborative 'instrumentalities of justice' and not business rivals" of the agency (*United States* v. *Ruzicka,* 329 U.S. 287, 295). The decision below disregards that scheme.

B. THE COURT OF APPEALS' CONCLUSION DENYING FDA JURISDICTION IS BASED ON ERRONEOUS PREMISES

The court of appeals rested its conclusion that FDA is without jurisdiction in all circumstances to adjudicate "new drug" status upon a series of erroneous premises: (1) that no procedure exists for agency consideration of the question; (2) that the agency should not be held to have the power to adjudicate "new drug" status because its determination would not be judicially reviewable; (3) that the structure of the Act compels the manufacturer to decide without benefit of an agency determination whether his product is a "new drug" and either market it without approval or concede such status by filing an NDA; and (4) that the inquiry into safety and efficacy undertaken when the agency acts upon an NDA is significantly different from that into "general recognition" of safety and efficacy underlying determination of "new drug" status. In our view, the court incorrectly assessed each of these factors, and none of them warrants the result it reached.

1. *The Agency May Determine "New Drug" Status in Proceedings Under Section 505 or in Declaratory Order Proceedings Under the Administrative Pro-*

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however, that it has primary jurisdiction over "new drug" status, safety and effectiveness, and it will continue to assert this position where appropriate.

cedure Act. It is our contention that the Third Circuit's decision in *CIBA Corporation* v. *Weinberger, supra* (No. 72–528), reflects the correct interpretation of the Act. There, the agency withdrew approval of an NDA held by CIBA for Ritonic Capsules. CIBA attacked the withdrawal in two separate judicial proceedings. It petitioned for review of the withdrawal order in the Second Circuit pursuant to Section 505 (h), and it filed a declaratory judgment action in a federal district court in New Jersey, claiming that its product is not now a "new drug" and therefore is exempt from the Act's requirements (J.A. 185–192). The district court dismissed the complaint (J.A. 214); the Second Circuit affirmed the agency's withdrawal order. *Ciba-Geigy Corp.* v. *Richardson,* 446 F.2d 466. On appeal from the dismissal of its district court action, CIBA contended in the Court of Appeals for the Third Circuit that neither the agency nor the Second Circuit on direct appeal of the agency's action, had jurisdiction to determine whether Ritonic Capsules are a "new drug" subject to the Act; rather, it claimed that it could litigate this issue in full in the district court. The Third Circuit held, however, that the agency necessarily is empowered to decide the threshold question as an incident of its power to approve or withdraw approval of NDAs and that its decision on that issue is reviewable in the court of appeals on direct appeal from the agency's order (J.A. 216):

> Inherent in the grant of administrative competency to conduct and decide new drug pro-

> ceedings is jurisdiction to decide whether the product in question in a given case is lawfully subject to such a proceeding. And, if the administrative agency takes jurisdiction, the same jurisdictional issue is present for judicial review on direct appeal from the administrative decision.
>
> In disapproving Ritonic Capsules the Commissioner and the Court of Appeals for the Second Circuit necessarily decided that the 1962 amendments of the Act were applicable to that product. * * * It is neither necessary nor appropriate that the District Court for the District of New Jersey entertain a separate suit by the loser in the administrative proceeding and in the direct appeal therefrom for a redetermination of the same question.

Under this approach, the agency serves as the primary forum for determining what is a "new drug" subject to its jurisdiction.

Of course *CIBA,* which correctly establishes the agency's subject-matter jurisdiction to deal with the "new drug" question, arose in the context of a proceeding for withdrawal of approval of an NDA. But even where the manufacturer has no NDA in effect or is not seeking approval for one, so that the determination of the "new drug" question would not be ancillary to any proceeding specifically prescribed by the Act, a procedure is available whereby the agency may determine the issue. The Administrative Procedure Act expressly enables FDA, like any other administrative agency, to issue "a declaratory order to terminate a controversy or remove uncertainty" (5

U.S.C. 554(e)). The present case illustrates an appropriate occasion for the exercise of the agency's declaratory order authority to resolve the controversy whether the respondent's drugs are in fact "me-too" copies of the products whose NDAs were withdrawn, and whether they are either effective or immune from the Act's efficacy requirements, by reason of the grandfather clause or otherwise. (A discussion of the appropriateness of initial agency consideration of these issues is set forth in point II, *infra*.)

An analogous situation was presented in *Frozen Food Express* v. *United States,* 351 U.S. 40, in which this Court held reviewable an order of the Interstate Commerce Commission determining that certain commodities were not exempt from regulatory requirements under the agricultural exemption to the Motor Carrier Act. The Court noted (351 U.S. at 44) that such an order is declaratory under the Administrative Procedure Act, rather than immediately coercive. Similarly, in *Red Lion Broadcasting Co.* v. *Federal Communications Commission,* 395 U.S. 367, 372–373, n. 3, which involved an application of the FCC's fairness doctrine, this Court ruled that since FCC could have conducted adjudicatory proceedings in which the licensee's compliance with the fairness doctrine would be an issue, "it could, under the Administrative Procedure Act, have issued a declaratory order in the course of its adjudication which would have been subject to judicial review."

Finally, FDA may, as in the case of over-the-counter drugs (see pp. 24–25, *supra*), promulgate pro-

cedures for rule-making under Section 701(a) (21 U.S.C. 371(a)) to classify categories of drugs as generally recognized as safe and effective, rather than dealing with each drug separately. Cf. *Abbott Laboratories* v. *Gardner*, 387 U.S. 136, 147, 149–152; *Ciba-Geigy Corp.* v. *Richardson*, 446 F. 2d 466 (C.A. 2), and authorities cited therein.

2. *Judicial Review of the Agency's "New Drug" Determination is Available.* Noting that the Act grants a right of direct appeal to the courts of appeals only from an order denying or withdrawing approval of an NDA (Section 505(h)),[11] the court below reasoned that "[i]t is not to be assumed that the Act confers an adjudicatory right on the Secretary from which no judicial review, however limited, is provided or allowed" (J.A. 268). But this is an erroneous premise. Review is available regardless of the form of order, so long as the order is administratively final.

If FDA's ruling on the threshold question of the Act's coverage is made in the context of an administrative proceeding that results in an order refusing (Section 505(d)) or withdrawing (Section 505(e)) approval of an NDA, that ruling is reviewable in the courts of appeals upon petition of the applicant-manufacturer under Section 505(h). Since that provision does not purport to limit the kinds of issues

[11] Section 505(h), J.A. 480, provides in part: "An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals * * * a written petition praying that the order of the Secretary be set aside. * * *"

the courts of appeals may consider in reviewing the agency's denials or withdrawals of approvals, the agency's determination of the threshold question whether the product involved is lawfully subject to the agency proceeding is, as the Third Circuit held in *CIBA,* subject to judicial review on direct appeal.

On the other hand, if the agency's order is not a denial or withdrawal within the court of appeals' jurisdiction under Section 505(h), but is instead an order declaring "new drug" status, it may be reviewed in the district court under the Administrative Procedure Act.[18] See *Citizens to Preserve Overton Park* v. *Volpe,* 401 U.S. 402; *Abbott Laboratories* v. *Gardner, supra; Frozen Food Express* v. *United States, supra.* That Act specifically provides that "final agency action for which there is no other adequate remedy in a court [is] subject to judicial review." 5 U.S.C. 704.

In *Abbott Laboratories,* drug manufacturers challenged FDA regulations prescribing certain labeling requirements for prescription drugs under Section 701(a) of the Act, 21 U.S.C. 371(a). Unlike regulations under Section 701(e) of the Act, which are subject, under Section 701(f), to direct review in the court of appeals (21 U.S.C. 371(f)), the Act provides no special procedure for review of such regulations. The government contended that the direct review procedure was exclusive and that other types of regulations were therefore unreviewable. This Court held that the provisions for direct review "were simply

[18] Jurisdiction in the district court to review the order would be based on 28 U.S.C. 1331 or 28 U.S.C. 1337.

intended to assure adequate judicial review of such agency decisions, and that their enactment does not manifest a congressional purpose to eliminate judicial review of other kinds of agency action." *Abbott Laboratories* v. *Gardner, supra,* 387 U.S. at 144. That review, the Court ruled, is available under the Administrative Procedure Act, 5 U.S.C. 701–704, and under the Declaratory Judgment Act, 28 U.S.C. 2201, so long as the agency's action is final and ripe for consideration. Compare *Toilet Goods Assn.* v. *Gardner,* 387 U.S. 158. Thus, under the rationale of *Abbott Laboratories,* (1) any manufacturer whose NDA is denied or withdrawn by the agency, may obtain direct review in the court of appeals under Section 505(h), including review of his product's "new drug" status; and (2) a final declaratory order by the agency, including any final declaratory determination of "new drug" status not otherwise within the direct review provisions of the Act, may be reviewed in the district court under the Administrative Procedure Act.

3. *The Act Does Not Compel the Manufacturer to Concede "New Drug" Status When Filing an NDA.* The court below attempted to buttress its conclusion that the agency may not determine its own jurisdiction by contending that the question of "new drug" status is never presented when an application for approval is filed. It reasoned that "[t]he very filing of the application is a concession and recognition by the applicant-manufacturer that the article is a 'new drug'" (J.A. 268). However, the source of this conclusion is not readily apparent. Nothing in the Act compels a

manufacturer who is uncertain whether its product is a "new drug" to choose between marketing the product without administrative approval, thus risking civil and criminal penalties, or making what the court below characterizes as a "concession" that the product falls within the Act by filing for approval under Section 505(b). Instead, the manufacturer may file a request for a determination that its product is not a "new drug," under the declaratory order procedures of the Administrative Procedure Act, and offer evidence in support of its contention."

An order making such a determination, or a general rule doing so for a class of drugs (see pp. 24–25, *supra*), becomes the basis on which the manufacturer orders his affairs. If FDA determines that the product is not a "new drug," it may be marketed without an approved NDA; if the agency determines that it is a "new drug" subject to the regulatory requirements of the Act, the manufacturer may pursue an application for approval before the agency, withdraw the product from the market in order to avoid the substantial civil and criminal sanctions against unauthorized products, or, where feasible, reformulate and relabel the product to bring it within a class of drugs generally recognized as safe and effective. Cf. *Frozen Food Express* v. *United States*, *supra*.

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[11] Since 1942, the agency, considering it had authority to determine "new drug" status, has issued opinions to manufacturers that particular drugs are or are not "new drugs." See pp. 6, 9, *supra*. Since "new drug" status is a jurisdictional question, the absence from the agency's application form of a space in which to raise the issue cannot be controlling, as the court below seems to have believed (J.A. 268).

One apparent difficulty with the reasoning of the court below is that, even if the manufacturer "concedes" that his product is a new drug by filing for approval, the agency's "acceptance" of this concession could not settle the jurisdictional question. Assuming the court is right that the agency is without power to decide the question, then if the agency denied the application or subsequently withdrew its approval, the court of appeals on review would either have to determine the "new drug" question *de novo* [50] or render a decision whose jurisdictional basis under the Act would be subject to relitigation in a district court action for declaratory judgment.[51]

4. *The "New Drug" Issue and the Safety and Effectiveness Issues Raise Substantially Similar Questions.* Finally, the court of appeals erred in relying (J.A. 268–269) for its conclusion upon the differences it perceived between the safety and effectiveness questions involved in an agency proceeding for approval or withdrawal of approval of an NDA (under Sections 505(d) and 505(e)), on the one hand, and the questions of "general recognition" of safety and effectiveness involved in the "new drug" determination (under Section 201(p)), on the other. In our view, the inquiry in either case is substantially similar, with resolution of the question turning upon expert scientific and medical judgment.

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[50] This would be a highly unusual procedure, since courts of appeals are not equipped to resolve factual issues *de novo*. Cf. 28 U.S.C. 2347(b).

[51] This is, in substance, petitioner's contention in *CIBA Corporation* v. *Weinberger*, *supra*, No. 72–528.

Thus, under the elaborate safety and effectiveness criteria spelled out in Section 505(d), the agency is expressly authorized to deny an application if it concludes that it has insufficient information to determine whether the drug is safe and effective for use by humans under the conditions prescribed. If the agency properly reaches such a conclusion, it would be a rare case indeed in which there could at the same time exist proper general recognition of safety and effectiveness sufficient to eliminate agency jurisdiction over the product under the "new drug" definition.

Furthermore, Section 505(d) directs FDA to deny approval where there is a lack of "substantial evidence" of effectiveness, which is defined in terms of clinical investigations "by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts * * * " that the drug will be effective as claimed. This basic theme of judgment by qualified experts precisely echoes Section 201(p)'s definition of a "new drug" as one "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use * * *." Under both provisions of the Act, therefore, the emphasis is on the expert knowledge and experience of scientists based upon carefully controlled clinical experimentation and backed by substantial support in scientific literature. Cf. *United States* v. *An Art. of Drug "Bentex Ulcerine"*, 469 F. 2d 875, 880 (C.A. 5). The substantial over-

lap in the content of the inquiries reinforces the conclusion that the regulatory scheme established by Congress encompasses administrative authority to make both sorts of determinations.[82]

Indeed, it is the position of FDA that as a general proposition there can be no general recognition of safety and effectiveness by experts where "substantial evidence" of effectiveness as defined by Congress is lacking. In other words, the kind of scientific support for claims of efficacy required to obtain approval of an NDA is generally a necessary condition to avoidance of "new drug" status (although not necessarily a sufficient condition, since a drug can be proved efficacious without there being a general recognition of this fact), so that a major part of the inquiry under both Section 201(p) and Section 505(d) is precisely the same.[83] See p. 12, *supra*.

C. THIS COURT HAS IN OTHER CONTEXTS RECOGNIZED THE BROAD POWERS OF ADMINISTRATIVE AGENCIES TO DETERMINE THEIR OWN JURISDICTION

The fact that Congress has not spelled out in so many words the authority of FDA to pass upon the question whether a product is a "new drug" does not mean it should be held to have excluded the agency

[82] Of course, we do not deny that in enforcement proceedings the district court must decide whether a product is a "new drug" subject to regulation, at least where the issue has not been litigated before the agency. See, *e.g.*, *Bentex Ulcerine*, *supra*. But the existence of such power in the courts is not inconsistent with its existence in the agency.

[83] The correctness of FDA's position on this issue is before the Court in connection with a companion case, *Hynson, Westcott and Dunning, Inc.* v. *Weinberger*, No. 72-414, and it will be briefed more fully there.

from the exercise of a function for which it is inherently well suited and which is vital to the effective administration of its responsibilities. Denial of the power to pass upon questions of "new drug" status would prevent FDA from dealing administratively with the problems presented by "me-too" copies of drugs whose NDAs have been withdrawn on efficacy grounds.[84] It would seriously undermine FDA's program of reviewing the status of and establishing standards for over-the-counter drugs. And it would crowd the courts with a large volume of litigation requiring *de novo* resolution of complex scientific issues. In a situation such as this, the Court, in the absence of an explicit Congressional directive, should inquire where Congress would prefer to have questions of this nature determined. We submit that the sensible answer is the expert administrative agency. That is how the Court has answered similar questions in the past.

Thus, in areas in which economic regulation has been to some degree applied ~~on~~ to an industry, expert administrative agencies have been held to possess broad powers to determine the scope of their own jurisdiction. Indeed, this Court has said that it may not, "in the absence of compelling evidence that such was Congress' intention, * * * prohibit administrative action imperative for the achievement of an agency's ultimate purposes." *Permian Basin Area*

[84] This assumes that the Court will agree with the government's position in the *USV* case (No. 72-666) that the grandfather clause does not exempt "me-toos" from the efficacy requirements of the Act.

Rate Cases, 390 U.S. 747, 780; cf. *United States* v. *Southwestern Cable Co.,* 392 U.S. 157; compare *National Broadcasting Co.* v. *United States,* 319 U.S. 190, 219, 220; *American Trucking Assns.* v. *United States,* 344 U.S. 298, 311.

This Court has recently observed that, where the question of an agency's threshold jurisdiction turns on the resolution of technical questions of fact of a kind arguably within the competence of the agency, it "should at least be requested to institute proceedings." *Ricci* v. *Chicago Mercantile Exchange,* No. 71-858, decided January 9, 1973 (slip op., p. 15). Even where it is claimed that administrative jurisdiction is lacking because a product is not being sold in commerce, the question is ordinarily to be resolved in the first instance by the agency. *Myers* v. *Bethlehem Corp.,* 303 U.S. 41, 50–51. Cf. *Oklahoma Press Pub. Co.* v. *Walling,* 327 U.S. 186, 210–211. "Authority to investigate the existence of violations accordingly include[s] authority to investigate coverage." *Id.* at n. 47. Similarly, the Court has held that whether a union is a "labor organization" *arguably* within the jurisdiction of the NLRB, or whether an electric system is subject to regulation by the FPC, are jurisdictional questions to be decided in the first instance by the agency. *Marine Engineers Beneficial Assn.* v. *Interlake S. S. Co.,* 370 U.S. 173, 185; *Federal Power Commission* v. *Louisiana Power & Light Co.,* 406 U.S. 621, 647.

No sound reason appears why Congress would deny this type of essential authority to an agency with

sweeping responsibilities for protecting the public health, while allowing it to agencies engaged in economic regulation. The statutory scheme of the Federal Food, Drug and Cosmetic Act shows that Congress did not so intend. Rather, in conferring on the agency comprehensive powers to perform its mission, it necessarily included the threshold power to decide whether products are "new drugs" over which it has jurisdiction.

II. THE DISTRICT COURT PROPERLY EXERCISED ITS DISCRETION IN REFERRING TO FDA THE QUESTION WHETHER RESPONDENTS' PRODUCTS ARE "NEW DRUGS" REQUIRING ADMINISTRATIVE APPROVAL

Since FDA has power to decide the "new drug" question, the court of appeals erred in setting aside the district court's referral of that question to the agency. The district court's referral was an appropriate exercise of the broad equitable discretion vested in the courts in declaratory judgment actions, and was in accordance with the principle that technical questions unsuited for judicial determination should, where possible, be resolved in the first instance by the appropriate regulatory agency.

The wisdom of the referral is apparent from examination of the issues raised in the declaratory judgment proceeding. Following the NAS–NRC finding of ineffectiveness, the agency here made an administrative determination that there is no substantial evidence that drugs containing pentylenetetrazol are effective. It therefore withdrew NDAs that had been approved prior to 1962, when safety had been the

sole criterion. This determination was not appealed and thus became final. However, the action directly affected only the three NDAs that were outstanding for products containing this drug. Many other manufacturers had products on the market that appeared, in FDA's view, to be mere copies of the drugs found ineffective. Since these "me-too" drugs had never been through the NDA process, there was no physical piece of paper for FDA to withdraw. But, in FDA's view, if these were in fact substantially the same drugs and were as ineffective as the pioneers, Congress wanted them removed from the market too.

After the respondents here had declined to participate in the NDA withdrawal proceedings and had been advised by letter from FDA that the agency, after the withdrawal of approval had become final, considered their products containing pentylenetetrazol to be "new drugs" that could not be marketed without an approved NDA, respondents brought this declaratory judgment action. They contended (1) that their products are not now "new drugs," and (2) that they are exempt from the efficacy requirements of the 1962 amendments by reason of the grandfather clause in Section 107(c)(4). J.A. 223–224. The factual issues presented vary somewhat depending on whether the government's interpretation of the grandfather clause and the "new drug" definition or that of the manufacturers is accepted, but, in either event, they are the kind of issues particularly suited to initial determination by the expert administrative agency.

The district court concluded that even though the "new drug" determination "can be made in this forum, the nature of the proof relevant to that issue makes the F.D.A. the more able arbiter of the question. * * * Evaluation of conflicting reports as to the reputation of drugs among experts in the field is not a matter well left to a court without chemical or medical background" (J.A. 256–257). It thus carefully explained its reasons for referring the matter to the agency. In contrast, the court of appeals noted respondents' claims concerning the differences between their own and the disapproved products but characterized them as only "questions of fact not relevant to the simple question of jurisdiction" (J.A. 264, n. 18).

The entire question of jurisdiction is not simple, however. For example, under the government's view of Section 107(c)(4),[35] a "me-too" product is considered "covered by" the "pioneer's" NDA, and therefore not grandfathered, if it is identical to or substantially similar or closely related to the pioneer in the chemical composition of one or more of its active components. If this view is correct, a factual issue arises whether respondents' products are in fact "me-toos." Here, the respondents have denied that their drugs are like the products whose NDAs were withdrawn, distinguishing them on the basis that the

[35] The government's position on the correct interpretation of the grandfather clause will be fully briefed and argued in two companion cases to the instant case, *Hynson* (No. 72–414) and *USV* (No. 72–666), which squarely present various aspects of the issue.

latter are intravenously administered or are a compound containing the additional ingredient reserpine.

Even if the government's interpretation of the grandfather clause were to be rejected, a factual issue arises whether, under clause (B) of Section 107(c)(4), respondents' products were generally recognized by qualified experts as safe in October 1962, or, under an alternative claim of current "old drug" status, whether they are today generally recognized by such experts as both safe and effective. As pointed out in point I(B)(4), *supra,* pp. 55–57, the resolution of such technical factual issues substantially overlaps the type of inquiry routinely undertaken by FDA in passing on NDAs.

Since these kinds of questions require determination of highly complex chemical, medical and pharmacological questions, which turn on expert evaluation of the state of scientific opinion and knowledge as to the products involved, they may appropriately be referred to expert agencies by a court. For as this Court recently observed, even "[w]hen there is a basis for judicial action, independent of agency proceedings, courts may route the threshold decision as to certain issues to the agency charged with primary responsibility for governmental supervision or control of the particular industry or activity involved." *Marine Terminal Association* v. *Rederi Transatlantic,* 400 U.S. 62, 68. This is merely an application of well established principles recognizing the specialized role of administrative agencies like FDA. As this Court observed in *Far*

East Conference v. *United States*, 342 U.S. 570, 574-575:

> * * * in cases raising issues of fact not within the conventional experience of judges or cases requiring the exercise of administrative discretion, agencies created by Congress for regulating the subject matter should not be passed over. This is so even though the facts after they have been appraised by specialized competence serve as a premise for legal consequences to be judicially defined. Uniformity and consistency in the regulation of business entrusted to a particular agency are secured, and the limited functions of review by the judiciary are more rationally exercised, by preliminary resort for ascertaining and interpreting the circumstances underlying legal issues to agencies that are better equipped than courts by specialization, by insight gained through experience, and by more flexible procedure.

This Court's recent decision in *Ricci* v. *Chicago Mercantile Exchange, supra,* directly supports the district court's decision to refer the "new drug" issue to FDA. That case, like this one, involved a claim for exemption from a statute. It was a private treble damage action under the Sherman Act in which the defendant claimed exemption from the antitrust laws on the ground that its conduct was justified by the requirements of a regulatory statute, the Commodities Exchange Act. This Court held that the exemption issue must be decided by the district court, but that in making this determination the trial judge should first refer the

case to the regulatory agency charged with administering the Commodity Exchange Act. Such a referral, this Court held, would be of material aid to the district court in determining the exemption issue, because that issue turns on questions of fact "that should be dealt with in the first instance by those especially familiar with the customs and practices of the industry and of the unique market place involved. * * * They are matters typically lying at the heart of an administrative agency's task * * *" (slip op., p. 16).

The present case is an even stronger one than *Ricci* for referral to the agency. The issue before the district court in the declaratory judgment proceeding concerns a claim for exemption from the requirements of a statute. This claim is based, not on a purported conflict of one statutory regime with another, as in *Ricci*, but on disputed interpretation of the language of the regulatory statute itself. Resolution of these questions turns on technical issues of the kind normally left for expert administrative resolution. The agency has not considered, in an administrative proceeding, the specific claims respondents made in the district court, because respondents never presented them to it. By affording respondents an opportunity to be heard on their claims before the agency, the district court has also given the agency the opportunity to reconsider its views respecting the marketability of respondents' drugs. If respondents' submission to the agency persuades it to alter its initial determination, there will be no need for further judicial consideration. If it does not, then the agency's decision with

respect to these particular drugs will provide a more solid footing for judicial consideration of the issues that remain in controversy. Cf. *Far East Conference* v. *United States, supra,* 342 U.S. at 574–575.

Thus the district court's referral to the agency of the "new drug" and grandfather issues was a reasonable and desirable accommodation of the functions of court and agency, wholly consistent with the flexible nature of the declaratory judgment remedy. Cf. *Kerotest Mfg. Co.* v. *C–O–Two Co.,* 342 U.S. 180, 183–184.

CONCLUSION

For the foregoing reasons the decision of the court of appeals should be reversed.

Respectfully submitted.

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-666

USV PHARMACEUTICAL CORPORATION, PETITIONER

v.

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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BRIEF FOR PETITIONER

OPINIONS BELOW

The opinion of the court of appeals (A. 466-73) is reported at 461 F.2d 223. The opinion of the district court (A. 463-66) is not officially reported, but is reprinted at CCH FOOD DRUG COSM. L. REP. ¶ 40,489.

JURISDICTION

The judgment of the court of appeals (A. 474) was entered on May 24, 1972. A petition for rehearing was denied on July 5, 1972. The Chief Justice extended until October 30, 1972, the time within which to file a petition for certiorari. The petition was filed on October 30, 1972, and was granted on January 8, 1973 (409 U.S. —). The jurisdiction of this Court rests upon 28 U.S.C. § 1254(1). *Abbott Labs.* v. *Gardner,* 387 U.S. 136 (1967).

STATUTES INVOLVED

Section 201(p) of the Federal Food, Drug and Cosmetic Act of 1938, 52 Stat. 1041, provided in pertinent part:

> (p) The term "new drug" means—
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> (1) Any drug the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or
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> (2) Any drug the composition of which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

The Drug Amendments of 1962, 76 Stat. 781, 788-89, 21 U.S.C. § 321(p), note foll. § 321, provide in pertinent part:

> Sec. 102. (a)(1) Section 201(p)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 (p)(1)), defining the term "new drug", is amended by (A) inserting therein, immediately after the words "to evaluate the safety", the words "and effectiveness",

and (B) inserting therein immediately after the words "as safe", the words "and effective".

(2) Section 201(p)(2) of such Act (21 U.S.C. 321(p)(2)) is amended by inserting therein, immediately after the word "safety", the words "and effectiveness".

Sec. 107. * * *

(c) * * *

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

The pertinent provisions of Section 505 of the Federal Food, Drug, and Cosmetic Act of 1938, 52 Stat. 1052, as originally enacted and in force until October 10, 1962, are set forth at pp 1a-3a *infra*.

QUESTIONS PRESENTED

The 1962 amendments to the Federal Food, Drug, and Cosmetic Act of 1938 expanded the statutory definition of "new drugs", for which a new drug application ("NDA") must be approved by the Food and Drug Administration in advance of marketing, to include drugs "not generally recognized as * * * effective * * *" in addition to those "not generally recognized * * * as safe * * *". A "grandfather" provision, however, exempted drugs already on the market which then were not "new drugs", as defined by the Act prior to amendment, and "not covered by an effective [new drug] application * * *".

The questions are:

1. Whether the "grandfather" provision applies to pre-1962 drugs which were never "new drugs" from the mo-

ment of their introduction and were never the subject of a new drug application, thus literally qualifying for "grandfathered" status under the precise terms of the provision, but which are "me-too" products comprised of the same principal ingredient as earlier products of the same manufacturer for which NDA's had originally been filed.[1]

2. Whether the "grandfather" provision applies to pre-1962 drugs which had been the subject of an NDA when first introduced, but which by the time of the 1962 amendments were concededly no longer "new drugs", and were being treated by both the manufacturer and FDA as no longer subject to the regulatory scheme applicable to NDA'd products.

STATEMENT

The history of the products involved. In late 1955 and early 1956 petitioner USV Pharmaceutical Corp. filed new drug applications ("NDA's") with the Commissioner of Food and Drugs for a line of five drug products containing citrus flavonoid compound, a natural chemical substance extracted from citrus fruit (A. 368, 371).[2] The

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[1] In this Court the government has confessed error with respect to the rationale of the ruling below in its favor on this question, "agree[ing] with petitioner that the distinction drawn [by the court of appeals] between USV's me-toos and those of its competitors is discriminatory and not supportable" (Resp. Mem. on Petition for Certiorari (hereafter "Resp. Mem."), p. 11 n.13). But, by urging affirmance on a ground repudiated by the court of appeals, the government raises a broader question, *i.e.*, whether the "grandfather" provision applies to any "me-too" products, whether or not made by the same manufacturer as the pioneer formerly NDA'd product (see *id.*, p. 6). Petitioner will address the government's proposed issue in the Argument portion of this brief, as well as the narrower question presented by the petition for certiorari.

[2] The products were CVP Capsules; CVP Syrup; CVP with Vitamin K Syrup; CVP with Vitamin K Tablets; and Duo-CVP Capsules.

recommended use of the products was, and continues to be, control of abnormal capillary permeability and fragility (A. 394, 396, 425).[3]

Under the pre-1962 statutory scheme then in force, an effective NDA was the legal prerequisite for marketing a "new drug",[4] that is, a drug which (1) was "not generally recognized by experts * * * as safe" for its intended uses or (2) if generally so recognized but only as a result of investigations, had not otherwise been used to a material extent or for a material time.[5] A filed NDA automatically became effective after sixty days (or one hundred-eighty days if so ordered by the Commissioner), unless within that time the Commissioner issued an order refusing to permit the NDA to become effective.[6] In the NDA the manufacturer was required to show that his product was in fact safe, and the Commissioner's decision not to take action constituted tacit ratification of such proof.

In the present case the Commissioner took no action to block the effectiveness of USV's citrus flavonoid new drug applications. They consequently became effective sixty

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[3] This is a condition of the capillary walls which may result in easy surface bleeding such as bruises (A. 384, 435, 442-43). The use of USV's citrus flavonoid products for this purpose is recommended to physicians only. While no prescription is required to purchase these products, they are described merely as "a supplementary source of bioflavonoids" in the labeling made available to the lay purchaser. (A. 389-90.)

[4] Federal Food, Drug, and Cosmetic Act of 1938, § 505(a), 52 Stat. 1052. As amended in 1962 (Drug Amendments of 1962, § 104(a), 76 Stat. 784, 21 U.S.C. § 355(a)), § 505(a) now requires that an "approval" of a new drug application be effective.

[5] Section 201(p), 52 Stat. 1041.

[6] Section 505(c), 52 Stat. 1052. As amended in 1962 (Drug Amendments of 1962, § 104(c), 76 Stat. 784, 21 U.S.C. § 355(c)), § 505(c) now requires the Commissioner affirmatively to approve the new drug application before a new drug may be marketed.

days after filing, and the products were accordingly placed on the market (A. 366, 368).

In 1957 USV developed two additional citrus flavonoid products, similar in composition and labeling to the five for which NDA's had become effective the preceding year (A. 368, 465).[7] After obtaining explicit advice from the Food and Drug Administration as to one of the proposed products [8] that it was "generally recognized as safe", and hence was not a "new drug" within the meaning of the statute, USV began to market these "me-too" drugs without filing NDA's therefor (A. 368).[9] This action was never challenged by the agency (A. 369).

In 1961 USV sought a comparable Food and Drug Administration ruling as to its originally NDA'd citrus flavonoid products (A. 299). In response, FDA advised that two of the NDA'd products "are not new drugs". As to the remainder, FDA replied that it had incomplete current marketing information on which to base a determination, but would be "pleased" to rule upon receipt of additional data. (A. 300-01.)

USV supplied the requested information within a month, noting its "recollection" that "a short time after the NDA

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[7] The new products were Bivam, and Duo-CVP with Vitamin K Capsules. No additional labeling directed to physicians recommending Bivam for abnormal capillary permeability and fragility was disseminated.

[8] No separate ruling was sought on Duo-CVP with Vitamin K Capsules.

[9] In the regulatory parlance, as the court of appeals found, a "me-too" drug is one substantially identical to a previously-marketed product for which an NDA has become effective (since 1962, has been approved) but which subsequently became generally recognized as safe (and, since 1962, as efficacious), with the result that the copy is not a "new drug" within the meaning of the statute and can therefore be marketed without an effective (since 1962, approved) NDA. See A. 470, 472.

became effective" (*i.e.*, in 1956-57) its citrus flavonoid products were no longer considered to be "new drugs". "Confirmation of the above" was requested. (A. 301.) FDA never responded.

It has traditionally been considered the responsibility of the manufacturer to decide, subject to severe penalties if he is later held to have decided incorrectly, whether his product is a "new drug" requiring pre-marketing approval by FDA.[10] Because the identical citrus flavonoid compound was contained in all USV bioflavonoid products, three of which FDA had expressly ruled were not "new drugs", USV concluded that the "not-new" status of all these products had been established, and thereafter discontinued filing with FDA the supplemental information then required by regulations[11] as to NDA'd products (A. 301-02, 451). Although FDA was thus fully aware of USV's position that the products were no longer "new drugs" within the meaning of the statute, and that the company was treating each of them as no longer subject to the regulatory scheme applicable to NDA'd products, this too was never challenged by the agency.

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[10] *Bentex Pharmaceuticals, Inc.* v. *Richardson*, 463 F.2d 363, 365-66 (4th Cir. 1972), *cert. granted*, 409 U.S. — (1973) (No. 72-555) (A. 260). See also Peter Barton Hutt, *Proper Classification of Products under the Federal Food, Drug, and Cosmetic Act*, p. 3 (unpublished paper presented at Annual Convention of the Federal Bar Ass'n, Miami, Fla., Sept. 4, 1969). ("The third, and final, general principle is that it is the primary and initial responsibility of the manufacturer of a product to determine the proper classification of his product, and to make certain that it meets all applicable legal requirements. It is in no instance necessary, and in most instances inadvisable, to ask the Food and Drug Administration for its opinion on the proper classification of the product. • • • It is • • • usually preferable for the manufacturer to exercise the obligation of proper classification given to him by the statute, rather than abdicating that responsibility to the Government.")

[11] Section 130.9, 25 Fed. Reg. 12595 (1960).

The Drug Amendments of 1962. In 1962, the Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act expanded the grounds upon which the marketing of a "new drug" could be prevented or terminated by FDA. Prior to 1962, a new drug application could be prevented from becoming effective, and its effectiveness could thereafter be suspended, only on grounds relating to safety.[12] The 1962 amendments required FDA, in deciding whether to approve or to revoke approval of new drug applications, to consider the evidence of efficacy as well.[13] At any time after the expiration of a two-year "grace period", moreover, FDA could initiate revocation proceedings as to pre-1962 NDA's which were still operative [14] and, after "due notice and an opportunity for hearing to the applicant", withdraw approval previously granted upon a finding "that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have * * *".[15]

The 1962 amendments also expanded the definition of "new drug" to cover drugs not generally recognized by experts as "safe *and effective*" for their intended uses.[16] However, as to certain products already on the market and generally recognized as safe, Section 107(c)(4) of the amending statute granted "grandfather" exemption from the definition of "new drug" as amended, and preserved the right of such products to remain on the market without advance FDA approval. To qualify for the Section 107

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[12] Sections 505(d), -(e), 52 Stat. 1052-53.

[13] Drug Amendments of 1962, §§ 102(c), -(d), 76 Stat. 781-82, 21 U.S.C. §§ 355(d), -(e).

[14] Drug Amendments of 1962, § 107(c)(3), 76 Stat. 788-89, 21 U.S.C. note foll. § 321.

[15] Drug Amendments of 1962, § 102(d), 76 Stat. 782, 21 U.S.C. § 355(e).

[16] Drug Amendments of 1962, §§ 102(a)(1), -(2), 76 Stat. 781, 21 U.S.C. § 321(p) (emphasis added).

(c)(4) exemption, it must be shown that the product "on the day immediately preceding the enactment date" (*i.e.*, October 9, 1962) satisfied three conditions: (A) that it was commercially used or sold in the United States, (B) that it was not a "new drug" as defined by the Act as then in force (*i.e.*, was "generally recognized * * * as safe" and had been used for a material time and extent), and (C) that it was not "covered by an effective [new drug] application" under the Act.[17]

Continued exemption of a "grandfathered" product from the FDA preclearance requirement does not mean that the public is unprotected against an ineffective drug. False or misleading efficacy claims constitute "misbranding" in violation of the Act, as they have since 1938, and subject the manufacturer to severe criminal and civil sanctions as well as seizure of his product and its removal from the market.[18]

The origins of the present litigation. In July 1968, relying upon an adverse report on the efficacy of one of USV's bioflavonoid products rendered by the National Academy of Sciences/National Research Council Drug Efficacy Study which FDA had commissioned following the 1962 amendments,[19] FDA initiated proceedings under the Act as amended[20] to revoke approval of the three citrus flavonoid NDA's held by USV. In light of FDA's

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[17] 76 Stat. 789, 21 U.S.C. note foll. § 321.

[18] § 502(a), 52 Stat. 1050, 21 U.S.C. § 352(a). *See Bentex Pharmaceuticals, Inc.* v. *Richardson*, note 10 *supra*, 463 F.2d at 367 (A. 262). See also note 151 *infra*.

[19] A. 290. The particular Drug Efficacy Study report relied on by FDA has since been condemned as "cryptic and conclusory, without any statement of supporting facts" (*USV Pharmaceutical Corp.* v. *Secretary of HEW*, 466 F.2d 455, 461 (D.C. Cir. 1972)).

[20] Section 505(e), 52 Stat. 1053, *as amended*, 21 U.S.C. § 355(e).

prior position with regard to the products, however, the company believed that each of its citrus flavonoid formulations satisfied the criteria for "grandfathered" status under Section 107(c)(4) of the 1962 amendments and that, under the pre-1962 definition of "new drug" which therefore remained applicable, the products were not "new drugs" for which an approved NDA was in any event required.

Petitioner therefore instituted the present action in the district court for a declaratory judgment to that effect against the Secretary of Health, Education and Welfare and the Commissioner of Food and Drugs, who are charged with the administration of the Food, Drug, and Cosmetic Act.[21] A stay of the administrative revocation proceeding for the pendency of the declaratory judgment action was sought from FDA.[22]

The decision of the district court. After a full evidentiary trial, the district court issued its findings and con-

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[21] Section 201(d), 52 Stat. 1040, *as amended*, 21 U.S.C. § 321(d); 21 C.F.R. § 2.120.

[22] The stay was denied, but no further action was taken by FDA to prosecute the revocation proceeding. In July 1970, contemporaneously with the setting of a trial date in the declaratory judgment action, FDA sought to revive the revocation proceeding by calling upon petitioner to establish its right to a hearing under "summary judgment" regulations which the agency had promulgated in the interim. Petitioner again moved for a stay pending disposition of the declaratory judgment action (A. 302-04). Eight days before trial in the district court was scheduled to begin, FDA denied the stay and entered a final order of revocation, refusing to allow petitioner to contest the matter further (A. 297-99, 304-05). The revocation order has since been set aside by the Court of Appeals for the District of Columbia Circuit for denial of "administrative due process", resulting from FDA's use of procedures which were "fundamentally defective • • • unsound and unfair" (*USV Pharmaceutical Corp.* v. *Secretary of HEW*, note 19 *supra*, 466 F.2d at 460, 461). No review in this Court was sought (see Resp. Mem., p. 4 n. 6).

clusions in the form of an Order and Memorandum Opinion (A. 463-66). FDA's challenge to jurisdiction was rejected on the authority of this Court's decision in *Gardner* v. *Toilet Goods Ass'n*, 387 U.S. 167 (1966) (A. 464). Proceeding to the merits, the court held that petitioner was correct as to all its citrus flavonoid products—both the "me-too" products for which no NDA had ever been filed, and also those products for which NDA's had become effective when the products were originally introduced.

The court found Clauses (A) and (B) of Section 107(c)(4) to be satisfied as to each of the products—they were on the market prior to the 1962 amendments (A. 464), and at that time they were not "new drugs" (A. 465). And as to the "me-too" products, the district court ruled that they "were never covered by effective new drug applications", thus qualifying under Clause (C) as well (A. 464).

As to the formerly NDA'd products, the court found that by the time of the 1962 amendments both petitioner and FDA were treating the products as no longer subject to the regulatory scheme applicable to NDA'd products. Thus, in a practical sense, the previously-approved NDA's had been effectively withdrawn by petitioner, and "none of the plaintiff's bioflavonoid products in question were covered by an effective NDA as of October 9, 1962." (A. 464-465.)

Clause (C) of Section 107(c)(4) was therefore satisfied in the case of the formerly NDA'd products as well, and the pre-amendment definition of "new drug" continued to apply (A. 463), under which the products were not "new drugs" (A. 462). The remedy for any misleading claims of efficacy, the district court concluded, thus continued to be in criminal, injunction and seizure actions for unlawful "misbranding", rather than in administrative denial or revocation of marketing authority by FDA (A. 463).

The decision of the court of appeals. On appeal, after summarily affirming the jurisdictional ruling below (A.

467),[23] the court of appeals considered separately the NDA'd and non-NDA'd drugs. Although both groups were found to satisfy Clauses (A) and (B) of Section 107 (c)(4), the court reversed the ruling of the district court under Clause (C) as to both the "me-too" and the formerly NDA'd products.

(a) Dealing first with the formerly NDA'd products, the court of appeals rejected the district court's findings that the NDA's "had been effectively and practically withdrawn and that accordingly the drugs were not covered by an effective NDA" on October 9, 1962 (A. 468). "The error in this reasoning", the court stated, "is that it assumes that a manufacturer may effect a withdrawal of an effective NDA, either by a formal notice or by discontinuing compliance with the reporting requirements for NDA'd drugs. * * * [H]e has no such right after approval of the application by the Secretary. At that point, only the Secretary can withdraw the approval." Since the Secretary had undertaken no action to withdraw approval of petitioner's applications, the formerly NDA'd products were still covered. (A. 469.)

The court of appeals additionally rejected an alternative theory which it thought to be implicit in petitioner's argument: that since all the products involved had concededly become "generally recognized * * * as safe" prior to October 9, 1962, they had ceased to be "new drugs" and therefore the previously issued NDA's were no longer needed or 'effective' ". This theory, the court said, "would make surplusage of requirement (C) in the exemption statute" and by thus treating (C) as a "nullity" would offend "the well settled rule of statutory construction that all parts of a statute are to be given effect if at all possible." (A. 469-70.)

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[23] The court of appeals invoked by reference the rationale it had set out in the companion case of *Bentex Pharmaceuticals, Inc.* v. *Richardson*, note 10 *supra*.

(b) The court acknowledged that a separate problem existed as to USV's two non-NDA'd "me-too" products. Under the plain language of Section 107(c)(4), the products were "grandfathered" since they were admittedly "generally recognized * * * as safe" from the outset and had *never* been "covered" by an effective NDA (A. 470). Moreover, most commentators, while admitting the "incongruity" of a result which would exempt "me-too" products from the amended definition of "new drug" but not their pioneer NDA'd products, considered the result "compelled by the literal language of the statute." FDA's contention to the contrary in the course of this litigation had already been "severely criticized and with considerable reason." The argument was "at variance with the uniform position [FDA] has taken over the years with regard to the nature of NDA's", which, simply stated, was the NDA is "personal" to drugs "as individual articles, not as collective groups". (A. 470-71.)

Yet, having thus concluded that "me-too" versions generally are embraced by Section 107(c)(4), the court of appeals ruled that petitioner's own "me-too's" are not. The court reasoned that petitioner's "me-too's" were "similar in formula and labeling" to its earlier NDA'd drugs; that these NDA's were "personal" to petitioner; and that the NDA's therefore "covered" not only the specific NDA'd products but also "all others like in formula" subsequently manufactured by petitioner. The two non-NDA'd products were thus also found to be derivatively ineligible for "grandfathered" status despite the literal language of the statute to the contrary. (A. 473.)

(c) Because each of petitioner's pre-1962 citrus flavonoid products is in all likelihood a "new drug" under the statutory definition as amended, the effect of the court's decision that the amended definition applies is to make an approved NDA prerequisite to the continued marketing of each product, whether or not an effective NDA was ever

necessary prior to 1962. The court conceded that "this conclusion places [petitioner] in a less favorable position than [other manufacturers] who may have copied its product prior to October 9, 1962". But the inequity thus created could be redressed, the court held, only by Congress. (A. 473.)

INTRODUCTION AND SUMMARY OF ARGUMENT

While the issues in this case involve solely the interpretation of the "grandfather" provisions of the Drug Amendments of 1962, those provisions are inextricably intertwined with other strands of the complex regulatory scheme established by Congress in the Federal Food, Drug, and Cosmetic Act. As has been said with reference to other sections of this "long and complicated" statute, the "grandfather" provisions "do not stand entirely separate and independent of the Act's structure."[24] Enacted against a background of almost twenty-five years of Food and Drug Administration interpretation and enforcement of the basic 1938 statute—a background with which Congress was made closely familiar through extensive committee hearings and reports on the proposed amendments—the 1962 "grandfather" provisions cannot be construed *in vacuo*. They must be read in the context of the entire regulatory structure erected by Congress in 1938, the substantive revisions made in 1962, and the purposes which the legislative history shows were intended to be served by those revisions as well as the alternative purposes which Congress considered and rejected.

In seeking to confine the 1962 "grandfather" provisions as narrowly as possible, the government does more than merely ignore the language of the statute expressly conferring "grandfathered" status upon pre-1962 products which, like petitioner's, were not then "covered by an effec-

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[24] *United States* v. *Sullivan*, 332 U.S. 689, 699 (1948) (Rutledge, J., concurring).

tive [new drug] application". It presses upon the court a construction which would distort the basic elements of the regulatory scheme devised by Congress in 1938 and continued in 1962. The government's proposed construction of the "grandfather" provisions would introduce fundamental inconsistencies and conflicts into the regulatory structure, and would nullify Congress' carefully considered 1962 decision (1) to continue to regulate "new drugs" differently from other drugs, and (2) to preserve the "old drug" status of products already on the market which, like those of petitioner, were not then being regulated under the 1938 statute as "new drugs".

The products involved in this case were all on the market prior to 1962, when the "new drug" regulatory provisions were expanded to include FDA pre-marketing review of drug efficacy as well as safety. Some of petitioner's products had previously been regulated as "new drugs", under the former statutory provisions for FDA pre-marketing review of safety; others had from the outset been "old drugs" generally recognized as safe, and therefore had always been regulated solely through the parallel system of civil and criminal remedies provided by Congress for dealing with such products rather than through the "new drug" provisions.

The 1962 amendments enlarged the statutory definition of the term "new drug", and in the absence of any "grandfather" provisions would have converted many "old drugs" then on the market into "new drugs" requiring Food and Drug Administration approval if their marketing were to continue. The legislative history of the 1962 amendments unambiguously demonstrates, however, that this was not Congress' purpose. Products already on the market and then being regulated not as "new drugs" but as "old drugs", like petitioner's here, were to continue to be regulated under the provisions of the Act applicable to "old drugs" so long as no new claims for the products

were made. This was accomplished by including in the 1962 statute a carefully worded "grandfather" clause limiting the applicability of the amended "new drug" definition.

The district court in the present case held that the "old drug" status of each of petitioner's pre-1962 products was protected by these "grandfather" provisions. The court of appeals held that none of the products was protected, but rested its ruling as to some of them on a ground now repudiated by the government, which seeks to defend the decision below on an alternative theory which both the district court and the court of appeals in this case have considered and rejected.

I. Two of petitioner's citrus flavonoid products were never the subject of effective NDA's. These products were introduced after other but similar products, manufactured by petitioner and originally marketed under effective NDA's, had become "generally recognized as safe" and therefore no longer were "new drugs". Petitioner marketed these "me-too" products from the outset as "old drugs"; they never were regulated under the provisions applicable to "new drugs".

As the court of appeals correctly observed, most "me-too" products such as petitioner's qualify for "grandfathered" status, because under the literal terms of the statute they were never "covered" by an effective NDA. But because petitioner itself had earlier marketed other citrus flavonoid products containing the same principal ingredient, under effective NDA's, the court of appeals held that, under the long-established doctrine that an NDA is "personal" to the manufacturer submitting the application, petitioner's effective NDA's "would cover all its products similar in formula, including those specifically described in its applications and all others like in formula."

This ruling that an NDA radiates out to all similar products of the applicant, even though competing manufacturers' "me-too" versions of the same drug are not

"covered", overlooks one of two co-equal aspects of the "personal NDA" doctrine—that the NDA is personal not only to the manufacturer but to the specific product described in the application as well. In this Court, the government concedes that the distinction drawn by the court of appeals on the basis of whether the manufacturer in question held the pioneer NDA is "discriminatory and not supportable", but urges that "grandfathered" status should be denied to *any* "me-too" product similar in composition and use to another product which itself was covered by an effective NDA, no matter by whom manufactured.

This broad proposition was properly rejected by the court of appeals as in conflict with "the consistent construction of the Act by the FDA for thirty years * * * which accords with the literal language of the Act * * * [and therefore] may only be changed by Congress itself." On their face, the "new drug" provisions of the statute apply solely to "the applicant" under an NDA; the statute has never conferred any procedural rights upon other manufacturers to participate in or to seek judicial review of the adjudicatory proceedings conducted by FDA to determine whether the showing necessary to market the product has been made, or whether marketing rights enjoyed under an NDA should be revoked. The Food and Drug Administration has repeatedly asserted, in a variety of contexts, that an effective NDA confers marketing authority on no one but the applicant, and only for the products precisely as described in the application.

Moreover, by now suggesting for the first time in the thirty-five year history of the Act that authority to market a "me-too" product without filing an NDA derives from a previous NDA for some other but similar product, the government ignores the critical statutory distinction between *evidence* of the product's safety (or efficacy), which must be shown to the satisfaction of the Food and Drug Administration by the manufacturer if his product is a "new drug" for which an NDA is required, and *general*

expert recognition of safety (or efficacy)—an entirely different standard which must be met if the product is sought to be marketed without an NDA as an "old drug." The government's present assertion further ignores the long-held position of FDA that, under the "new drug" provisions of the statute, all variations in the dosage form, quantity, and combinations in which a product may be manufactured must be separately considered in deciding whether a particular variation is a "new drug" and in determining whether its marketing should be allowed.

These crucial elements of the regulatory scheme—which would be turned topsy-turvy if the government's present construction of the "grandfather" provisions were accepted—were expressly communicated to Congress by FDA during the legislative consideration of the 1962 amendments. The wholly "personal" character of an effective NDA, both as to the applicant as manufacturer and as to the precise form of the product described in the NDA, was a fundamental, unquestioned premise upon which Congress acted when it adopted the "grandfather" provisions. Moreover, Congress' understanding of this premise, and its acceptance of it for the future as well as in construing the basic 1938 statute, is manifest from other provisions in the 1962 amendments which are integrally related to the "new drug" regulatory scheme. In these circumstances, the government's conceded "reinterpretation" of the nature and effect of a pre-1962 effective NDA would work an unsupportable alteration of the fundamental structure of "new drug" regulation established by Congress.

Nor would such a "reinterpretation" be warranted by anything in the "purposes" of the 1962 amendments. Apart from the fact that nothing in those purposes could retroactively alter the meaning of the statute as enacted in 1938, the purpose which is relevant to this case is the one which led Congress to amend the definition of "new drug". That purpose, explicitly reiterated throughout the legislative

history, was not to impose "new drug" regulatory controls on existing claims for products already on the market which, like those of petitioner, were then being regulated solely as "old drugs". It was, rather, to insure that future claims for such products, and all claims for products subsequently introduced (whether made in the initial marketing or at some time thereafter), would be regulated under the scheme applicable to "new drugs" if the product were not generally recognized as both safe and effective for that claim. The government's apparent premise that expansion of the "new drug" category to include pre-existing "me-too" products would be desirable, from a regulatory standpoint, furnishes no warrant for judicial enlargement of the amended definition of "new drug" beyond what Congress intended to accomplish, and in contravention of the express terms of the "grandfather" provisions.

II. Although the court of appeals was thus clearly correct in rejecting the broad proposition advanced by the government as to "me-too" products, and erred in that regard only in excluding petitioner's "me-too's" from the scope of its ruling, the court misapprehended the nature of the "new drug" regulatory scheme in also holding that petitioner's formerly NDA'd products were outside the scope of the "grandfather" provisions.

Congress' purpose never extended to the imposition of "new drug" controls on existing claims for products already on the market which were not then being regulated as "new drugs". And the district court found on the undisputed facts that petitioner's actions after its original NDA's had become effective—actions which were affirmed or acquiesced-in by FDA—amounted in practical terms and legal effect to withdrawal of the NDA's, with consequent termination of NDA coverage, prior to the enactment of the 1962 amendments.

The court of appeals, apparently misled by its assumption that the acronym "NDA" stands for "New Drug Approval" rather than for "New Drug Application", con-

cluded that withdrawal of the *NDA*, by petitioner, was foreclosed by the power of FDA to withdraw *approval* under Section 505(e) of the statute as amended in 1962. But the statute has never empowered FDA to terminate the coverage of an NDA on the ground that the drug involved has become an "old drug" which, because it has become "generally recognized as safe" through use for a material time and extent, need no longer be subject to "new drug" regulation. The Food and Drug Administration's authority under Section 505(e) permits it to act only for the very opposite reason—that there is no longer evidence showing the product to be safe (or, under the amended statute, efficacious).

If an effective NDA which has become superfluous may be retired on that ground (and common sense says it may and should), then the procedure for doing so must be inferred from the whole scheme and purpose of the statute. And it strains both reason and common sense to hold that though the "no longer new" status of a product has been (a) asserted by the manufacturer, (b) ratified by FDA, (c) acted upon by the manufacturer (in discontinuing all supplemental NDA filings) and (d) put into practical effect by FDA (in no longer imposing NDA controls), the product is nevertheless still "covered by an effective [new drug] application" for purposes of the "grandfather" provisions because there has been no resort to the formal revocation-of-approval procedures of Section 505(e), which can be initiated only by FDA, extend only to the precisely opposite situation, and therefore could not have been invoked by petitioner to terminate the coverage of its NDA's on the ground that the products were no longer "new".

The district court was therefore correct in construing the "grandfather" provisions of the 1962 amendments to embrace petitioner's formerly NDA'd but no longer "new" products, as being among those not "covered by an effective NDA" when the amendments were enacted. As thus con-

strued, no part of the 1962 "grandfather" provisions is surplusage. To the contrary, the government's proposed construction, taken as a whole, would in practical terms read the provisions entirely out of the statute, by confining their operation to those products already on the market when the basic Act was enacted in 1938 and, accordingly, already protected by the original 1938 "grandfather" clause which was left undisturbed by Congress in 1962.

In sum, the government's effort in this case to rewrite the 1962 "grandfather" provisions, so as to win from this Court what FDA requested but was unable to obtain from Congress, is justified by none of the familiar aids to statutory construction. It would result only in a regulatory hodgepodge bearing no resemblance to the carefully balanced scheme which Congress established in 1938 and continued in 1962 without basic structural departures.

ARGUMENT

I. THE COURT OF APPEALS CORRECTLY CONSTRUED THE "GRANDFATHER" PROVISIONS OF THE 1962 AMENDMENTS IN ACCORDANCE WITH THEIR TERMS, SO AS TO PRESERVE THE ORIGINAL DEFINITION OF "NEW DRUG" FOR PRE-1962 "ME-TOO" PRODUCTS FOR WHICH NO NDA'S HAD EVER BEEN FILED BY THEIR MANUFACTURERS, AND ERRED ONLY IN DISCRIMINATORILY DENYING THE BENEFIT OF THIS RULE TO PETITIONER.

A. The Government Has Abandoned Its Dispute with Petitioner as to the Facts and Has Confessed Error as to the Rationale of the Decision Below on the Legal Issue.

As described above (p. 6 *supra*), Bivam and Duo-CVP with Vitamin K Capsules contain the same citrus flavonoid compound as certain earlier products of petitioner for which NDA's had originally been filed and become effective. They were first marketed by petitioner in 1957 after securing an informal opinion from the Food and Drug Administration as to one of them that the product was "generally recognized as safe" and, therefore, marketable

without an effective NDA. From that time on, FDA never challenged the marketing of these two products without effective new drug applications, and petitioner made no attempt to comply with any of the requirements in the statute or in FDA regulations which would have been applicable to "new drugs" which were "covered by effective NDA's".

Both the district court and the court of appeals in this case concluded that these two pre-1962 "me-too" products literally meet each of the three prerequisites for "grandfathered" status under Section 107(c)(4), so as not to become "new drugs" by reason of the amendment to the definition of that term. Each was marketed in the United States prior to enactment of the amendments; at that time each was generally recognized as safe and hence was not a "new drug"; and, under the literal terms of the statute, neither was "covered by an effective [new drug] application".

1. The marketing of these and petitioner's other citrus flavonoid products prior to 1962, in satisfaction of Clause (A) of Section 107(c)(4), was stipulated at trial.[25] It was further stipulated that in 1962, and at all times since, all these products have been generally recognized by qualified experts as not pharmacologically toxic in that a normal individual would not develop adverse reactions.[26] In the courts below, however, the government insisted that despite this stipulation the products were not "generally recognized as safe" within the meaning of the statute, and thus fail to qualify under Clause (B) of Section 107(c)(4), because (a) they were not generally recognized as efficacious,

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[25] A.366. The extent to which the products had been used, also stipulated (*ibid.*), was found by the district court to be "substantial" (A. 464).

[26] A. 370-71; see also Brief for Appellants Richardson *et al.*, p. 53, *USV Pharmaceutical Corp.* v. *Richardson*, No. 71-1596, 4th Cir.

and (b) in certain limited circumstances allegedly present here, a drug is unsafe for use if it is ineffective for such use.[27]

But the evidence at trial overwhelmingly demonstrated that, in any event, the necessary factual predicate for such an argument here had not been established.[28] On its own terms, moreover, the theory has never extended to "in-

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[27] It was urged that "where a drug is offered for use in the treatment of life-threatening disease", the use of "an ineffective drug * * * in the treatment of a disease where there exists a efficacious drug which is not used * * * could result in serious harm" (Brief for Appellants Richardson *et al.*, note 26 *supra*, p. 54). In its testimony before Congress on the 1962 amendments FDA had stressed that even under its view of existing law, the safety of a non-toxic drug could be construed to include efficacy *only* where the disease involved is "life-threatening" (*Hearings on S.1552 Before the Subcomm. on Antitrust and Monopoly of the Senate Comm. on the Judiciary*, 87th Cong., 1st Sess., pt. 5, at 2588 (testimony of HEW Secretary Ribicoff); *Hearings on H.R. 11581 et al. Before the House Comm. on Interstate and Foreign Commerce*, 87th Cong., 2d Sess. 64 (same)). This limitation was recognized in both of the committee reports on the 1962 amendments (S. Rep. No. 1744 (pt. 1), 87th Cong., 2d Sess. 15; H. Rep. No. 2464, 87th Cong., 2d Sess. 3). Both in 1964 and again in 1969, moreover, FDA confirmed that its theory of the pre-1962 law was applicable only under such circumstances (*Hearings on Drug Safety Before a Subcomm. of the House Comm. on Government Operations*, 88th Cong., 2d Sess., pt. 1, at 150, 183-86 (testimony of FDA Commissioner Larrick); *Hearings on Drug Efficacy Before a Subcomm. of the House Comm. on Goverment Operations*, 91st Cong., 1st Sess. 228 (testimony of FDA Commissioner Ley).

[28] The sole condition for which these products have been recommended is, as the district court found (A. 465), abnormal capillary permeability and fragility (A. 394, 396, 425), which was never suggested to be "life-threatening". It was shown that no alternative drug has been available for that condition (A. 439, 440, 442), and that petitioner's products have not been recommended to the exclusion of treatment for any underlying more serious condition (A. 428).

nocuous" drugs [29]—the very term used by the district court to summarize the testimony on the safety of these products (A. 465).[30] Indeed, FDA had advised Congress in 1962 that these very citrus flavonoid products of petitioner were among those to which the safety-includes-efficacy theory was inapplicable.[31]

Thus, the district court summarily rejected the government's contention that in 1962 these products were still in fact "new drugs" (A. 465), and the court of appeals found "no dispute that such drugs met criteria (A) and (B), as set forth in the 'grandfather clause' " (A. 468).[32] In this court the government accepts these findings, conceding that "after a full district court trial, there are now no disputed issues of fact".[33] The sole remaining controversy relates to the final prerequisite for Section 107(c)(4) "grandfather" protection, that in 1962 the products were not "covered by an effective [new drug] application".

2. As noted above, both the district court and the court of appeals concluded that each of petitioner's two "me-too"

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[29] *Hearings on S.1552,* note 27 *supra,* at 2944 (letter from HEW Secretary Ribicoff to Senate Judiciary Committee Chairman Eastland); S. Rep. No. 1744 (pt. 1), note 27 *supra,* at 16; *Hearings on Drug Efficacy,* note 27 *supra,* at 228 (testimony of FDA Commissioner Ley).

[30] In addition there was direct testimony that qualified experts would not regard the theory as applicable here (A. 426, 437, 439-40), and that, as the district court found (A. 462), the products in fact were and are generally recognized by qualified experts as safe for their intended use (A. 424-25, 437, 443). As to the efficacy of the products, the district court found that the expert witnesses called by petitioner had testified that "the plaintiff's bioflavonoids were not only safe but quite effective" (A. 465).

[31] *Hearings on S. 1552,* note 27 *supra,* at 2584 (testimony of HEW Secretary Ribicoff).

[32] Specifically as to the two "me-too" products, the court of appeals explained that they "were generally recognized as safe • • • on October 9, 1962" (A. 470).

[33] Resp. Mem., p.6 n.9.

products "meets literally the criteria for exemption" (A. 470). Unlike the district court, however, the court of appeals denied "grandfathered" status to these two products, and it did so by reading into the statute a fourth prerequisite which does not appear in its text. The court of appeals held that a drug otherwise qualifying for "grandfathered" status is ineligible for that status if it is equivalent to some other drug—a "pioneer" drug—previously marketed by the same manufacturer and which at any time prior to October 9, 1962, was the subject of an effective new drug application.

The government, confessing in this Court that the position of the court of appeals "is discriminatory and not supportable" because it would deny to petitioner's "me-too" drugs the "grandfathered" status conferred upon bioflavonoid products identical to those of petitioner but manufactured and marketed as "me-too's" by others,[34] nevertheless seeks to uphold the result as to Bivam and Duo-CVP with Vitamin K Capsules on a sweeping theory repudiated by both courts below. Under this twice-discredited theory, in determining the applicability of Section 107(c)(4) the "coverage" of an effective NDA for a single "pioneer" drug would include in its penumbra all "me-too" drugs which are "basically the same pharmacologically", regardless of the identity of the manufacturer or the method of production, even if the "me-too" was generally recognized as safe up to and including October 9, 1962 and was never itself NDA'd.[35]

Such coverage is said to flow from those "items [in the NDA] which looked to the safety of the drug as a generic article" as opposed to those giving " 'personal' information on the methods, facilities and controls which a particular company would use in its manufacture, processing and packaging."[36] (Resp. Mem., p. 10). The premise

[34] Resp. Mem., p.11 n.13.

[35] Resp. Mem., p.10.

[36] *Ibid.*

for this conclusion is that the NDA's [for pioneer drugs] "presumptively established * * * that the formulation and use covered was marketable as a general class of product",[37] so that "issuance of the pioneer's NDA normally provided the predicate for lawful marketing of the copies."[38]

B. The Theory on Which the Government Seeks Affirmance of the Judgment Below Is Refuted by the Terms and Context of the "New Drug" Provisions of the Statute and Their Contemporaneous and Consistent Construction by the Food and Drug Administration.

The government's effort to save the decision below as to Bivam and Duo-CVP with Vitamin K Capsules is fundamentally at odds with the nature of the "new drug" regulatory scheme enacted by Congress. Nothing to support it can be found in either the language or the legislative history of the 1938 Act or the 1962 amendments. Not merely does the government's present argument "represent a change" (as the Solicitor General candidly acknowledges),[39] but indeed a complete *volte-face* from FDA's own contemporaneous and long-held interpretation of the 1938 statute—of which the 1962 Congress was made well aware by the agency—as confining the "coverage" of an NDA solely to the manufacture of the precise product described, solely by the applicant, in solely the manner described in the NDA.

That the government now overreaches is "clear from the language of the Act, its legislative history, its early administrative interpretation and the construction placed upon it by Congress in subsequent enactments" (*Great Northern R. Co.* v. *United States,* 315 U.S. 262, 277 (1942)).

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[37] *Id.,* p. 11.

[38] *Id.,* p. 10. See also Petition for Certiorari, p. 14, *Richardson* v. *Bentex Pharmaceuticals, Inc.,* No. 72-555, *filed* October 5, 1972, *cert. granted,* 409 U.S. —— (1973).

[39] Resp. Mem., p. 11.

1. The government's present position is inconsistent with the intent of Congress as reflected in the precisely limited language of Section 505.

The original language of Section 505,[40] re-enacted in 1962 without change in this regard, explicitly reflects the purely "personal" nature of an effective (now, approved) NDA. Proceedings to suspend the effectiveness of an NDA were commenced by "due notice and an opportunity for hearing *to the applicant*" (Section 505(e)). Orders refusing to permit an NDA to become effective, or suspending effectiveness, were served either in person or by registered or certified mail "addressed *to the applicant or respondent*" (Section 505(g)). Judicial review was expressly authorized solely on "appeal * * * taken by *the applicant*"—originally to the district courts and since 1962 to the courts of appeals (Section 505(h)).

(a) If in 1938 Congress had intended an effective NDA to "cover" products and manufacturers not named in the application, presumably it would have recognized the adverse effect on others of an order suspending the NDA's effectiveness by giving such others—as it did in contemporaneous statutes—adequate notice, opportunity for hearing, notice of final orders, and judicial review.[41] The Food,

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[40] 52 Stat. 1052-53, *as amended*, 21 U.S.C. § 355. For the convenience of the Court, the original text of § 505 is reprinted in pertinent part at pp. 1a-3a *infra*.

[41] *Compare, e.g.*, Investment Company Act of 1940, § 40(a), 54 Stat. 842, *as amended*, 15 U.S.C. § 80a-39(a) ("Orders * * * shall be issued only after appropriate notice and opportunity for hearing. Notice to the parties * * * shall be given by personal service * * * or by registered mail * * *. Notice to interested persons, if any, other than parties may be given in the same manner or by publication in the Federal Register"); Communications Act of 1934, § 402(b), 48 Stat. 1093, *as amended*, 47 U.S.C. § 402(b):

> "Appeals may be taken from decisions and orders of the [Federal Communications] Commission * * * in any of the following cases:
>
> (1) By any applicant * * * whose application is denied * * *.

Drug, and Cosmetic Act itself contains detailed provisions for formal on-the-record rulemaking, with Federal Register publication of notices and orders, on matters where Congress intended the results of trial-type proceedings to be broadly applicable throughout an industry.[42] Yet as originally enacted, and never changed, Section 505 made no provision for notice to any other person than the applicant; for an opportunity for any other person to be heard; for notice of the final order to any other person; or for judicial review at the behest of any other person.

Nor were these provisions broadened in 1962. The same Congress which made "grandfather" protection under Section 107(c)(4) turn upon "coverage" by an effective NDA demonstrated its continued understanding of the purely "personal" coverage of an NDA by re-enacting, intact, the limited notice, hearing, service, and judicial review provision of Section 505, with their exclusive emphasis upon "the applicant" as the person adversely affected by a revocation order.[43]

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(2) By any applicant for renewal or modification • • • whose application is denied • • •.

(3) By any party to an application for authority to transfer • • • whose application is denied • • •.

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(5) By the holder of any construction permit or station license which has been modified or revoked • • •.

(6) By any other person who is aggrieved or whose interests are adversely affected by any order • • • granting or denying any application described in paragraphs (1)-(4) • • •".

[42] Section 701, 52 Stat. 1055-56, *as amended*, 21 U.S.C. § 371.

[43] Federal Register publication of a § 505(e) notice of opportunity for hearing, now required by FDA regulations (21 C.F.R. § 130.14), was not provided for until after the controversy over the 1962 "grandfather" provisions had arisen (29 Fed. Reg. 7020 (1964)). Even today there is no explicit provision for Federal Register notice of final orders approving, refusing to approve, or withdrawing approval of NDA's, but merely a practice employed since about 1963.

(b) By transferring statutory review jurisdiction under Section 505(h) to the courts of appeals, while simultaneously re-enacting the provision which confers standing to seek statutory review solely upon "the applicant", the 1962 Congress further evidenced its understanding that an NDA is purely "personal" to the applicant and "covers" no one else. As the government recognizes in its argument to this Court in *Bentex*,[44] Section 505(h) confers jurisdiction on the courts of appeals only in accordance with its precise terms, which confine review to appeals by "the applicant".[45] Review of an order revoking approval of a pioneer NDA could thus be sought by a "me-too" manufacturer only in the district court, if at all, a multiplicitous pattern for judicial review which can hardly have been intended by Congress. Since it is equally inconceivable that Congress would have (or could constitutionally have) intended entirely to bar judicial review of a revocation order at the behest of a "me-too" manufacturer if his product were "covered" by another firm's NDA, the only reasonable inference is that Congress believed that only the applicant and his particular product as described in the application would be adversely affected by a revocation order, *i.e.*, was "covered" by the NDA.

(c) To say the least, moreover, serious constitutional problems of administrative due process would plainly be

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[44] Petition for Certiorari, p. 18, *Richardson* v. *Bentex Pharmaceuticals, Inc.*, No. 72-555, *filed* October 5, 1972, *cert. granted*, 409 U.S. —— (1973).

[45] See *Wholesale Grocers' Ass'n* v. *FTC*, 277 Fed. 657 (5th Cir. 1922); *Waller* v. *FTC*, No. 11,741, 4th Cir., December 6, 1967 (unreported order); *PepsiCo, Inc.* v. *FTC*, 1972 CCH Trade Cas. ¶74,260 (2d Cir. 1972) (Friendly, J.). *Cf. American Federation of Labor* v. *NLRB*, 308 U.S. 401, 404 (1940); *Cheng Fan Kwok* v. *INS*, 392 U.S. 206 (1968); *Turkel* v. *FDA*, 334 F.2d 844 (6th Cir. 1964); *Upjohn Co.* v. *Finch*, 303 F. Supp. 241, 248 (W.D. Mich. 1969). This principle was already well established at the time of the original 1938 Act. *Pote* v. *Federal Radio Commission*, 67 F.2d 509 (D.C. Cir. 1933) (*en banc*).

presented if the Act, in its original form or as amended, were construed as authorizing the Food and Drug Administration to revoke a manufacturer's authority to market his pre-1962 "me-too" product without giving him notice or hearing. This much is apparently recognized by FDA itself in the recently promulgated "regulation" which sets forth the agency's plan for implementing its new position.[46]

On the explicit premise that "an identical, similar or related drug product is covered by the NDA's for the basic product", the new regulation states in effect that NDA approval revocation orders, past as well as future, will be construed as having withdrawn marketing authority from products "identical, similar or related to" the specific products for which the NDA's were allowed to become effective. Presumably to overcome the absence of any provision in either the original or the amended Section 505(e) for extending notice and an opportunity for hearing to "me-too" manufacturers, the regulation prospectively engrafts on the statute an entirely unsanctioned procedure purporting to give such manufacturers in the future "the same opportunity as the applicant to submit data and information, to request a hearing, and to participate in any hearing".[47]

Putting aside as not presently germane the possible inadequacy even of this procedure under the Due Process Clause and the Administrative Procedure Act,[48] and the

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[46] *Applicability of DESI Notices and Notices of Opportunity for Hearing to Identical, Related, and Similar Drug Products,* § 130.40, 37 Fed. Reg. 23187 (1972).

[47] § 130.40(a), 37 Fed. Reg. 23187 (1972).

[48] According to the regulation (*ibid.*), "it is not feasible for the Food and Drug Administration to list all products which are covered by an NDA and thus subject to each notice" of opportunity for hearing on a proposal to revoke approval of an NDA which (under the regulation first promulgated in 1964, note 43 *supra*)

further constitutional difficulties in applying the new policy retrospectively to NDA revocation orders previously issued under entirely different procedures,[49] the new scheme is a classic instance of an agency's " 'attempted addition to the statute of something which is not there' " (*Commissioner* v. *Acker*, 361 U.S. 87, 93 (1959)).[50] If some such procedure would be necessary to preserve the constitutionality of the statute as construed by FDA, which the government presumably would concede, then the failure of the statute itself to provide one is persuasive evidence that Congress never intended the Act to be so interpreted. *Cf. FPC* v. *Tuscarora Indian Nation*, 362 U.S. 99, 113 (1960). And in no event should this Court reach out for an interpretation of the Act which would, by reason of the absence of any statutory provision for notice and hearing to non-applicants, put its constitutionality in doubt. *Cf. United States* v. *National Dairy Prods. Corp.*, 372 U.S. 29, 32 (1963); *Joint Anti-Fascist Refugee Comm.* v. *McGrath*, 341 U.S. 123, 165 (1951) (Frankfurter, J., concurring).

It should further be noted in this connection that marketing a "new drug" without an approved NDA in violation

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appears in the Federal Register. Yet FDA concedes that "there will be * * * areas where the judgment of experts must determine the applicability of the efficacy findings", in light of complex technical considerations as well as "any other information available on the action or properties of the drug" (37 Fed. Reg. 23185 (1972)). and suggests that any manufacturer in doubt as to whether FDA considers his product to be "covered" by another's NDA should request an advisory opinion on the matter (§ 130.40(b), 37 Fed. Reg. 23187 (1972)).

[49] Notices of opportunity for hearing in prior NDA revocation proceedings (*e.g.*, the one with respect to the products involved in this case, A. 296) recited merely the boilerplate formalism that the "applicant and any interested person who would be adversely affected by an order" could request a hearing, whereas notices issued subsequent to the new regulation explicitly refer to "manufacturers of identical, similar or related drugs".

[50] Quoting *United States* v. *Calamaro*, 354 U.S. 351, 359 (1957).

of Section 505, which under FDA's view would be the posture of a "me-too" manufacturer when approval of the pioneer NDA of another manufacturer is revoked, is a criminal offense under the Act.[51] Acceptance of the government's present position would thus effectively create by administrative regulation a new crime not prescribed by Congress. The patent Fifth Amendment problems need not be elaborated.

2. Both prior to and since the 1962 amendments, FDA has consistently construed the "coverage" of an effective NDA to be purely "personal" to the named applicant and to his product as described therein.

(a) Prior to the enactment of the 1962 Drug Amendments, there had been no suggestion either by the Food and Drug Administration or in Congress that an effective NDA "covered" anything but the specific drug described in the application as manufactured by the applicant himself. To the contrary, as early as 1941 FDA publicly advised that an NDA applied solely to a particular product of a particular manufacturer:

> "This section [505], in our judgment, applies to drugs as individual articles, not as collective groups. We have been repeatedly asked by drug manufacturers and others whether it is necessary to file an application for, let us say, sulfapyridine, when other manufacturers have already placed sulfapyridine on the market. It is our interpretation of the Congressional intent that each manufacturer of sulfapyridine or any other drug must file his own application * * *."[52]

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[51] See §§ 301(d), 303, 52 Stat. 1042, 1043, *as amended*, 21 U.S.C. §§ 331(d), 333.

[52] Statement of Theodore G. Klumpp, M.D., Chief, Drug Division, Food & Drug Admin., June 23, 1941, quoted in CCH FOOD DRUG COSM. L.REP. ¶ 71,051.09, at p. 72,039.

This restrictive view, well understood and fully accepted by industry and the bar,[53] was never relaxed. In 1960 the the Commissioner warned manufacturers that "counterfeit" drugs (manufactured as copies of existing trademarked drugs and intended to be palmed off as the original product) were for the most part "potent new drugs" and therefore required to undergo "the safety clearance procedures required for new drugs".[54] FDA's position was that a manufacturer wishing to market a drug identical to another drug, previously marketed under an effective NDA, must file his own NDA unless the product had come to be generally recognized as safe after use for a material time and extent.

"Me-too" drugs differ from "counterfeits" in that they are honestly marketed under their own names or as untrademarked "generics" (frequently at lower prices than the trademarked originals). But although their marketing might be under license from the original manufacturer if valid patents or trade secrets are involved, in other cases the original product or process was never patented, or its patent protection may have expired. And absent the consent of the original applicant, in no event has any element of the NDA—"generic" or otherwise—been thought to be the basis for marketing the "me-too". As noted in 1957, for example, FDA

> "has interpreted the statute to confer a proprietary interest in those holding effective new-drug applica-

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[53] See, *e.g.*, Kleinfeld, *New Drugs and the Durham-Humphrey Amendment*, 12 FOOD DRUG COSM. L.J. 617, 623 (October 1957) (* * * suppose one manufacturer submits a supplemental new-drug application under Section 505 for the switch [from prescription to over-the-counter availability]. This must be held in secrecy. If granted, he will, of course, have a real advantage over his competitors [marketing a similar product] until they prepare and submit their supplemental new-drug applications and the government ultimately acts on these applications").

[54] HEW Release, HEW-034, Oct. 13, 1960, quoted in CCH FOOD DRUG COSM. L. REP. ¶ 71,051, at p. 72.040.

> tions, and feels that the only way by which another can benefit from such an application is by the express consent of the person who filed it or of his duly appointed successors in interest. Failing to obtain such consent, clinical research must be conducted anew as if the conclusions shown by such research had never been proved." [55]

Thus, far from constituting or even "presumptively establishing" the right of competing manufacturers to market "me-too" products, as the government now argues (Resp. Mem., pp. 10, 11), the character of the NDA was authoritatively and consistently interpreted to have precisely the opposite effect. And this established administrative interpretation of NDA "coverage" as excluding rather than authorizing "me-too" manufacturers of "new drugs" has consistently been adhered to by the Food and Drug Administration even after the 1962 amendments. Not only does FDA require the filing of an NDA by each "me-too" manufacturer of a "new drug" "in order that we may control the labeling, the advertising that surrounds the drug, the manufacturing process that is going to be employed",[56] but reliance upon the pioneer NDA even to establish the "generic" safety and efficacy of the product is generally prohibited. As the Commissioner of Food and Drugs testified in 1967:

> "* * * under the policy FDA has followed since 1938, clinical data submitted to FDA by one firm cannot be utilized by a second firm wishing to market the same compound." [57]

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[55] Duckworth, *Some Drug Observations on the Federal Food, Drug, and Cosmetic Act*, 12 FOOD DRUG COSM. L.J. 300, 304 (May 1957).

[56] *Hearings on Present Status of Competition in the Pharmaceutical Industry Before the Subcomm. on Monopoly of the Senate Select Comm. on Small Business*, 90th Cong., 1st Sess., pt. 2, at 744 (testimony of FDA Commissioner Goddard).

[57] *Id.* at 821.

> "All the clinical trials, additional subjects studied, all the pre-clinical animal data has to be duplicated." [58]

In the words of FDA's chief counsel at that time, recently echoed by his successor, the NDA scheme presents "an individual licensing situation [rather than] a rulemaking situation".[59]

Indeed, not only reliance upon another manufacturer's NDA or some part thereof, but even mere access to it, has consistently been denied by the Food and Drug Administration. FDA has never deviated from its view that everything in the NDA file—"generic" or otherwise—is confidential and unavailable for inspection by would-be competitors or the public.[60]

It is therefore clear that from the very outset FDA has construed Section 505 of the 1938 Act as confining the "coverage" of an effective NDA to the applicant himself,

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[58] *Id.* at 744.

[59] *Id.* at 749 (HEW Ass't Gen. Counsel Goodrich); *id.*, 92d Cong., 2d Sess., pt. 22, at 8531 (HEW Ass't Gen. Counsel Hutt).

[60] *Hearings on Present Status of Competition,* note 56 *supra,* at 745-46, 748; *id.,* 92d Cong., 2d Sess., pt. 22, at 8531-32; 37 Fed. Reg. 9130 (1972) ("Since 1938, FDA has taken the position that such data ordinarily represent valuable commercial property and trade secrets that must be retained as confidential and may not be disclosed to the public"). Even under the pending proposal to expand public disclosure of FDA files (37 Fed. Reg. 9128 *et seq.* (1972)), safety and efficacy data in an approved NDA would generally remain confidential as "highly valuable material, since the law provides that a competitor cannot market or use the drug without first submitting such data and information to FDA for approval" (*id.* at 9130). The only exceptions (absent "extraordinary circumstances") would be for NDA'd products that "are 'old drugs' which do not require premarketing approval"; that are "me-too" drugs for which FDA now says an NDA, but only an abbreviated one, is necessary; and that have been removed from the market through revocation of the NDA approval. 37 Fed. Reg. at 9130.

giving no marketing authority to anyone but the applicant, and then only for the precise product described. Great weight should be given to this well-documented practice, both as the contemporaneous and long-standing interpretation of the Act by the agency charged with its administration (*e.g., Udall* v. *Tallman*, 380 U.S. 1, 16 (1965))[61] and as the agency's own contemporaneous understanding of the scope and impact of its orders allowing NDA's to become effective.[62]

(b) Nor is the controlling force of FDA's established interpretation impaired by its present assertion to the contrary for purposes of the "grandfather" issue. This Court has dealt with similar administrative turnabouts:

> "Against the [agency's] prior longstanding and consistent administrative interpretation its more recent *ad hoc* contention as to how the statute should be construed cannot stand."

United States v. *Leslie Salt Co.*, 350 U.S. 383, 396 (1956). And, in fact, FDA itself at first interpreted Section 107(c)(4) to embrace both pre-1962 "me-too's" and also their formerly NDA'd but "no longer new" pioneers,[63] and only

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[61] "Furthermore, the [agency's] interpretation gains much persuasiveness from the fact that it was the [agency] which suggested the provisions' enactment to Congress" (*United States* v. *American Trucking Ass'ns, Inc.*, 310 U.S. 534, 549 (1940). See note 147 *infra*.

[62] *Cf. Carnation Co.* v. *Pacific Westbound Conference*, 383 U.S. 213, 220-21 (1966); *Persian Gulf Outward Freight Conf.* v. *FMC*, 375 F.2d 335, 339 (D.C. Cir. 1967); *Swift & Co.* v. *FMC*, 306 F.2d 277, 281 (D.C. Cir. 1962).

[63] Interview with Deputy FDA Commissioner Harvey reported in F-D-C REPORTS ("THE PINK SHEET"), February 4, 1963, pp. 1-2. For the Court's convenience, the report of the interview is reproduced at pp. 4a-5a *infra*.

belatedly reversed its position in attempted reliance upon the theory presently advanced.[64]

The sole justification advanced by FDA for this diametric reversal of position on the "coverage" of a pre-1962 NDA is that the "statutory purpose" of the 1962 amendments "necessitated reconsideration" of the interpretation previously given to the 1938 Act.[65] But nothing in the 1962 legislation, no matter what its purpose, could retroactively change the meaning of the prior enactment (*Gemsco, Inc.* v. *Walling*, 324 U.S. 244, 265 (1945); *SEC* v. *Capital Gains Research Bureau, Inc.*, 375 U.S. 180, 199-200 (1963)).

As we show elsewhere in this brief, moreover, there is no evidence that in 1962 a different approach was intended by Congress even for the future. The Congress which enacted Section 107(c)(4) in 1962 was fully advised of the construction which had been placed upon the 1938 Act,[66] and not only failed to express the slightest dissatisfaction with that construction but evidenced continued adherence to it, both in the re-enacted portions of the "new drug" provisions[67] and in other portions of the amendments as well.[68]

Indeed, FDA's interpretation of the Act, as amended, has consistently been to the same effect as its traditional view

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[64] See PROCEEDINGS, FDA CONFERENCE ON THE KEFAUVER-HARRIS DRUG AMENDMENTS AND PROPOSED REGULATIONS, February 15, 1963, pp. 39-41, 42-43 (Gov't Printing Office 1963); Interview with Deputy FDA Commissioner Harvey, reported in F-D-C REPORTS ("THE PINK SHEET"), February 18, 1963, p. S-2. For the Court's convenience, the report of the interview is reproduced at p. 6a *infra*.

[65] Resp. Mem., p. 11.

[66] Pp. 45-46 *infra*.

[67] Pp. 27-29 *supra*.

[68] Pp. 47-51 *infra*.

when the "grandfather" clause is not under discussion.[69] And as recently as 1967 the agency rebuffed critics of its traditional position by insisting that the requirement of a complete NDA (including "generic" elements) from every "me-too" manufacturer was so firmly established that any change would have to come from Congress.[70]

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[69] (a) *Refusal to allow "me-too" manufacturers of "new drugs" to rely upon a pioneer NDA.* See *Hearings on Present Status of Competition,* note 56 *supra,* at 743-49, 754-56, 761, 821 (testimony of FDA Commissioner Goddard) (discussed at pp. 34-35 *supra*). The proposed revision of FDA's regulations on disclosure of NDA data makes clear that manufacturers wishing to market "me-too" versions of future NDA'd products will continue to be denied access to the "generic" safety and efficacy data in the pioneer NDA, until the pioneer product is no longer a "new drug" requiring a complete NDA, and that nothing in the pioneer NDA will "constitute the full reports required by statute for a competitor to obtain approval for an identical product" (37 Fed. Reg. 9131 (1972)). (b) *Records and reports.* The 1962 amendments to § 505 empowered FDA to promulgate regulations requiring regular and special reports to the agency "in the case of any drug for which an approval of an application filed pursuant to this section is in effect" (§ 505(j), 76 Stat. 782, 21 U.S.C. § 355(j)). But FDA has never suggested that "me-too" manufacturers were subject to this provision; to the contrary, the regulations apply merely to "the applicant" in the case of post-1962 drugs (21 C.F.R. § 130.13), and for pre-1962 drugs to "each applicant for whom a new drug application or supplement • • • became effective" (21 C.F.R. § 130.35)). (c) *Repackagers.* As late as 1970, FDA was unsuccessfully urging that a mere repackager of drugs purchased from the NDA applicant was required to file his own NDA in order to market "the very tablets manufactured" under the NDA held by his source (*United States* v. *Kaybel, Inc.,* 403 F.2d 1346, 1347 (3d Cir. 1970)).

[70] *Hearings on Present Status of Competition,* note 56 *supra,* at 744.

3. The government's assertion that "me-too" products were "covered" by effective NDA's filed by other manufacturers is inconsistent with the underlying principles of the Food, Drug, and Cosmetic Act.

The basic structure of the "new drug" regulatory scheme forecloses the premise on which the government has erected its present argument. Contrary to that premise, the right to market a "me-too" product without an effective NDA has never derived from an effective NDA filed by some earlier manufacturer or for some earlier product. As the court of appeals recognized (A. 472), marketability rests solely upon the fact that, through use for material time and extent, as manufactured and marketed by others, the drug involved has become generally recognized as safe (and, since 1962, as effective) and therefore is not a "new drug" within the meaning of the statute. *Cf. United States* v. *An Article of Drug * * * "Mykocert"*, 345 F. Supp. 571, 575 (N.D. Ill. 1972).

(a) The fact that an NDA has been allowed to become effective as to one manufacturer has never meant that the safety of the drug has become "generally recognized" so as to permit its marketing by another without filing an NDA of his own. As the Chief of FDA's New Drug Section wrote in 1949, whenever the statutory definition of "new drug" is applicable an NDA must be filed, even as to "drugs for which one or two new drug applications may be effective and which may be on the market":

> "The fact that an application or two applications have been permitted to become effective and that the drug is commercially available does not of necessity mean that the drug is *generally* recognized as safe for use. Rather, it means that in the opinion of the Administrator of the Federal Security Agency [of which FDA was then a component], that is to say, the medical officers of the New Drug Section, the evidence of safety for use offered by the applicant is adequate to justify a positive conclusion. But 'general recognition' is not possible until the drug has been used for a

> material time or to a material extent so that it has become generally known. In addition, in most cases the evidence on which such a positive conclusion is reached consists of observations which may be as yet unpublished by the investigators, and, therefore, not generally known to the 'experts.' "[71]

The distinction between *evidence* of safety and *general recognition* of safety is fundamental to the scheme of the "new drug" provisions of the statute.[72] It contradicts and undermines this fundamental statutory distinction, regularly insisted upon by FDA, for the government now to suggest that any element in an effective NDA "presumptively established" the marketability of the products by anyone other than the applicant, or that an effective NDA "covered" anything but the specific product as manufactured by him.

(b) It is only by ignoring the role of those elements in the NDA which are concededly "personal" to the applicant and the particular product, moreover, that the government can maintain its present position. For the "personal" elements have been central to the "new drug" regulatory scheme ever since the original enactment of the statute in 1938. If it were in fact true that "issuance of the pioneer's NDA normally provided the predicate for lawful marketing of the copies" (Resp. Mem., p. 10), then at least an NDA limited to these "personal" elements would have been required from each "me-too" manufacturer and for each "me-too" variation.

As originally enacted, Section 505 required each new drug application to include a list of the drug's compo-

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[71] Nelson, *New Drug Requirements of the Federal Food, Drug, and Cosmetic Act*, 4 FOOD DRUG COSM. L.Q. 227, 229 (June 1949) (emphasis in original).

[72] *E.g.*, *AMP, Inc.* v. *Gardner*, 389 F.2d 825 (2d Cir.), *cert. denied*, 393 U.S. 825 (1968).

nents;[73] a statement of its composition;[74] and "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug".[75] These requirements were carried forward in 1962 without change.[76]

The regulations promulgated by FDA, even prior to 1962, have always required still more details concerning the particular facilities and processes to be utilized by the applicant for the particular product involved. For example, the regulations in force at the time of the 1962 amendments required the NDA to include,

> "[i]f the applicant does not himself perform all the manufacturing, processing, packing and control operations, his statement identifying each person who will perform a part of such operations and designating the part; and a signed statement from each such person fully describing the facilities and controls he uses in his part of the operations directly or by reference." [77]

Full information was required as to serial numbers applied to raw material lots; the number of individuals checking weight or volume of ingredients as used in each manufacturing batch; "an explanation of the exact significance of any batch control numbers"; and all other details of the particular manufacturing procedures to be

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[73] Section 505(b)(2), 52 Stat. 1052.

[74] Section 505(b)(3), 52 Stat. 1052.

[75] Section 505(b)(4), 52 Stat. 1052.

[76] 76 Stat. 781, 21 U.S.C. § 355(b)(2)-(4).

[77] Section 130.4(e)(4)(b)(ii), 21 Fed. Reg. 5578 (1956). A similar provision was applicable with regard to the methods used by such third persons (§ 130.4(e)(4)(a)(iii), 21 Fed. Reg. 5578 (1956)). Equivalent provisions are currently in force (21 C.F.R. § 130.4(e)(2), ¶ 8(f)).

employed.[78] On-site inspection was required where, in FDA's judgment, a written description would not alone suffice.[79]

The particular dosage unit and form of a drug, as well as its particular combination of ingredients, have always been similarly relevant in FDA's evaluation of the drug's safety. Current administrative regulations which date from the enactment of the 1938 Act state, for example, that "the newness of a drug may arise by reason (among other reasons) of * * * (2) The newness for a drug use of a combination of two or more substances, none of which is a new drug. (3) The newness for drug use of the proportion of a substance in a combination * * *. * * * (5) The newness of a dosage, or method or duration of administration or application * * *."[80] According to FDA, timed-release dosage forms of "old drugs" may in some circumstances be "new drugs" by reason of the "possibility of unsafe overdosage if such products are improperly made and the active ingredients are released at one time or over too short a time interval".[81]

If under these criteria a particular formulation of the product is a "new drug", an NDA or supplemental NDA has been required, showing all details for that particular formulation. At the time of the 1962 amendments these included "the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug

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[78] Sections 130.4(c)(4)(b)(iv),-(vi),-(xi), 21 Fed. Reg. 5578 (1956.) The current requirements on these matters are in 21 C.F.R. § 130.4(c)(2), ¶¶ 8(e),-(j),-(o).

[79] Sections 130.6, 25 Fed. Reg. 12595 (1960). The current equivalent is at 21 C.F.R. § 130.6.

[80] C.F.R. § 130.1(h), first promulgated in 3 Fed. Reg. 1847 (1938).

[81] 21 C.F.R. § 3.512, first promulgated at 24 Fed. Reg. 3756 (1959).

in the form in which it is to be distributed"; "the methods used in processing and packing each proposed dosage form"; "a representative sample or samples of the finished dosage form(s) proposed in the application and employed in the clinical investigations"; and "a representative sample or samples of finished market packages of each dosage form of the drug prepared for initial marketing, and if any such sample is not from a commercial scale production batch, in addition such a sample from a representative commercial scale production batch".[82]

Even after the NDA becomes effective, variations in these respects have been required not merely to be reported but to be approved in advance. The regulations in force now and at the time of the 1962 amendments require each applicant under an effective NDA to submit a supplemental NDA "for any change beyond the variations provided for in the [original] application (including changes in the scale of production such as from pilot-plant to production batch) that may alter * * * the identity, strength, quality, or purity of the drug * * *."[83] Only if the product was no longer "new", and the applicant's "me-too" variation was not itself a "new drug", was the applicant free to market the variation without an effective supplemental NDA therefor.[84]

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[82] Sections 130.4(c)(3),-(4)(a)(ii), 21 Fed. Reg. 5578 (1956); §§ 130.4(c)(5)(a)(i),-(ii), 26 Fed. Reg. 2595 (1961). Today a separate NDA must be filed for each dosage form of a "new drug" (21 C.F.R. § 130.4(d)(ix)).

[83] 21 C.F.R. § 130.9(a)(2), first promulgated in 21 Fed. Reg. 5579 (1956).

[84] Section 130.9(e), 25 Fed. Reg. 12595 (1960). This provision was first promulgated in 21 Fed. Reg. 5579 (1956), and was deleted, without notice (compare the notice of proposed rulemaking at 29 Fed. Reg. 2790 (1964)), only after the controversy with respect to the 1962 "grandfather" provisions had arisen (29 Fed. Reg. 7020 (1964)).

The reason for requiring such information, and its review by FDA, both in the original NDA and on a continuing basis, is obvious. Every ingredient of a drug product may affect its safety.[85] The quantities of particular ingredients in a dosage unit, the relative proportions of each ingredient, and the method of administration are equally relevant to safety.[86] And to evaluate the safety of a drug as produced by a particular manufacturer it is necessary to evaluate, in the words of the regulations, "the adequacy of the manufacturing, processing, and packing methods to determine and preserve the identity, strength, quality, and purity of the drug".[87] As FDA itself noted in its comments to the Senate Judiciary Committee on the bill which became the Drug Amendments of 1962, "the methods, facilities and controls used by a particular drug manufacturer bear importantly on the safety of the drug".[88]

(c) Despite the importance to the public of the regulatory measures governing these "personal" aspects of manufacturing products covered by effective NDA's, at no time prior to 1962 did the Food and Drug Administration ever suggest that the manufacturer of a "me-too" product was required to file an NDA with respect thereto, or to wait for such an NDA to become effective before commencing

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[85] The fatal properties of "Elixir Sulfanilimide", which were responsible for the original enactment of the "new drug" provisions in 1938 (see note 147 *infra*), were contributed by the "supposedly inert" solvent or carrier for the therapeutic ingredient. Nelson, note 71 *supra*, 4 FOOD DRUG COSM. L.Q. at 227.

[86] *Id.* at 230.

[87] Section 130.4(a), 21 Fed. Reg. 5577 (1956).

[88] Letter from HEW Secretary Ribicoff to Senator Eastland, dated September 13, 1961, in *Hearings on S. 1552*, note 27 *supra*, at 2943. See also *Hearings on Present Status of Competition*, note 56 *supra*, at 755-56 (1967 testimony of FDA Commissioner Goddard to the same effect).

marketing. To the contrary, the regulations in 1962 did not require supplemental NDA's for "me-too" variations marketed even by the pioneer applicant, if the product was no longer "new" (*i.e.*, was generally recognized as safe) and the variation was not itself a "new drug".[89]

"Me-too" products nevertheless could not lawfully have been marketed without such controls had they been required, which would have been the case if the authority for their marketing was an effective NDA. The Food and Drug Administration practice of not imposing such controls thus confirms the basic principle, hitherto accepted by all, that "me-too's" were marketed as "old drugs" on the authority of general recognition of their safety, and demonstrates that the predicate for the present argument that they were covered by the NDA's approved as to pioneer manufacturers is wholly unsupportable.

4. Congress was expressly advised by FDA in the course of considering the 1962 amendments that an effective NDA was purely "personal" to the applicant and, while significantly amending the "new drug" provisions, left them unchanged in this respect when it incorporated the concept of "coverage" by an effective NDA into the "grandfather" provisions of Section 107(c)(4).

Congress would in any event be presumed, absent contrary evidence, to have intended the "grandfather" provisions of Section 107(c)(4) to be construed with reference to the law as it then stood. *St. Louis I.M. & S.R. Co.* v. *United States*, 251 U.S. 198, 207 (1920). But if there were any doubt in this instance as to the legislative intent, it would be resolved by the clear and direct notice which Congress was given by the Food and Drug Administration itself that NDA's were purely "personal".

(a) The formal report of the Department of Health, Education and Welfare on S. 1552, the bill which became

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[89] Section 130.9(e), 25 Fed. Reg. 12595 (1960).

the Drug Amendments of 1962, was a letter from HEW Secretary Ribicoff to Senate Judiciary Committee Chairman Eastland. The letter unequivocally stated, in describing the "new drug" regulatory scheme then in force, that:

> "If two or more manufacturers propose to market the same 'new drug' each must file a clearance application, the underlying reason being that the methods, facilities, and controls used by a particular drug manufacturer bear importantly on the safety of the drug".[90]

The same premise was implicitly reflected in other FDA testimony on S. 1552. As originally introduced by Senator Kefauver, S. 1552 would have initiated the licensing of each and every drug manufacturer on a product-by-product basis.[91] The Food and Drug Administration opposed this provision, on the grounds that the "personal" elements of an effective NDA already included the equivalent of such a licensing system for "new drugs" and that all other drugs could adequately be controlled if the agency were given authority to promulgate regulations defining "good manufacturing practices" enforceable in post-marketing seizure, injunction and criminal proceedings.[92]

The clear premise of this testimony was that all drugs being manufactured outside the scope of the "personal" elements in an effective NDA were "old drugs", as to which the proposal for judicially enforceable "good manufacturing practice" regulations was necessary in order to insure the integrity of manufacturing facilities, processes, and controls. It would have been entirely inconsistent with this premise for Congress to have thought that any products then on the market were "covered by effective

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[90] *Hearings on S. 1552*, note 27 *supra*, at 2943.

[91] Section 4(a)(13), S.1552, 87 Cong., 1st Sess.

[92] *Hearings on S. 1552*, note 27 *supra*, at 2591 (testimony of HEW Secretary Ribicoff).

NDA's" except those specifically being regulated through the "personal" elements of an effective NDA.[93]

(b) The construction contemporaneously put upon a statute by its administrators "carries most weight when the administrators participated in drafting and directly made known their views to Congress in committee hearings" (*Zuber* v. *Allen*, 396 U.S. 168, 192 (1969); see also *Perkins* v. *Matthews*, 400 U.S. 379, 391-94 (1971)). Having thus been told in 1962 that NDA's were purely "personal", each manufacturer of a "new drug" being required to file his own NDA, Congress (1) re-enacted the heavily-amended "new drug" provisions without change in this regard, and (2) employed the concept of "coverage by an effective NDA" in the "grandfather" provisions of Section 107(c)(4). The Food and Drug Administration can hardly now suggest that Congress nevertheless had something else silently in mind. *Farmers Educational & Coop. Union* v. *WDAY, Inc.*, 360 U.S. 525, 533 (1959).

5. The terms of the 1962 amendments demonstrate Congress' recognition of the purely "personal" character of the NDA, and explicitly distinguish the "generic" certification regulations by which the safety and efficacy of antibiotic drugs are controlled.

Finally, Congress' reliance upon the Food and Drug Administration's long-held view as to the purely "personal" coverage of an effective NDA was reflected in the 1962 amendments not merely in the re-enactment of Section 505 without change in this respect, but also in the amendments relating to the antibiotic regulatory provisions and to the control of animal feed.

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[93] See, *e.g.*, 108 Cong. Rec. 21057 (remarks of Representative Schenk, who was the author of the amended "good manufacturing practices" provision) ("Before any manufacturer is permitted to make a new drug he must file complete details of his manufacturing process with the Food and Drug Administration").

(a) *Antibiotics.* As amended in 1962, Section 507 of the Act directs FDA to promulgate regulations of general applicability establishing such standards of identity, potency, quality and purity as necessary to insure the safety and efficacy of antibiotic drugs, and requires FDA certification of all such drugs on a batch-by-batch basis.[94] Antibiotic drugs "subject to Section 507" are exempt from the NDA requirements of Section 505.[95] Provision is made for regulations exempting any antibiotic "drug or class of drugs" from the batch certification requirement when "not necessary to insure safety and efficacy of use".[96]

As originally enacted Section 507 applied solely to penicillin products, to which four specifically named additional antibiotics were subsequently added by legislation.[97] In 1962 the provision was expanded to include all present and future antibiotics.[98] The use of generally applicable regulations promulgated pursuant to the on-the-record rulemaking provisions of the Act to establish the "generic" elements of safety and efficacy was continued, however. The result is that, unlike manufacturers of other drugs requiring pre-marketing scrutiny, who have "private licenses", the manufacturers of antibiotic drugs "have

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[94] Section 507(a), 59 Stat. 463, *as amended*, 21 U.S.C. § 357(a). See *United States* v. *An Article of Drug* • • • *Bacto-Unidisk*, 394 U.S. 784, 785-87 (1969).

[95] Section 507(e), 59 Stat. 463, *as amended*, 21 U.S.C. § 357(e).

[96] Section 507(c), 59 Stat. 463, *as amended*, 21 U.S.C. § 357(c). Exemption is also authorized for antibiotic drugs manufactured for storage, processing, labeling or repacking by another, for use in manufacturing other drugs, and for investigational use (§ 507 (d), 59 Stat. 463, *as amended*, 21 U.S.C. § 357(d)).

[97] 61 Stat. 21 (streptomycin); 63 Stat. 409 (aureomycin (renamed chlortetracycline by 67 Stat. 389), chloramphenicol, and bacitracin).

[98] Drug Amendments of 1962, §§ 105(a)-(b), 76 Stat. 785, 21 U.S.C. §§ 357(a), -(b).

public regulations in the form of a monograph so once the drug is approved anyone can make the drug." [99]

Thus, a manufacturer proposing to market an antibiotic already on the market need file merely the equivalent of the "personal" data in an NDA.[100] For it is the regulations which establish for all manufacturers the marketability of particular classes of antibiotic drugs.

Prior to 1962, the statute was not explicit as to the regulatory status of antibiotic drugs exempted from batch certification, beyond the reverse implications of the provision exempting from the requirements of Section 505 "any drug subject to Section 507". The 1962 amendments clarified this ambiguity by explicitly excluding from the Section 505 exemption any "new drug exempted from the requirements of this section [507] * * * pursuant to regulations".[101] To permit compliance with the NDA requirements of Section 505 for an antibiotic "drug or class of drugs" thus exempted by regulation from Section 507, a proviso was added to Section 507(e) that:

> "for purposes of section 505, the initial request for certification, as thereafter duly amended, pursuant to section 507, of a new drug so exempted shall be considered a part of the application filed pursuant to section 505(b) *with respect to the person filing such request and to such drug* as of the date of the exemption." [102]

Like the "grandfather" provisions of Section 107(c)(4), this proviso first appeared in the version of S.1552 reported

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[99] *Hearings on Present Status of Competition*, note 56 *supra*, 92d Cong., 2d Sess., pt. 22, at 8531 (testimony of HEW Ass't Gen. Counsel Hutt).

[100] The procedural regulations prescribing the data required to be filed by a new manufacturer are at 21 C.F.R. § 146.2(b).

[101] § 105(e), 76 Stat. 786, 21 U.S.C. § 357(e).

[102] *Ibid.* (emphasis added).

by the Senate Judiciary Committee. It clearly reflects, we submit, the Committee's and Congress' understanding that, unlike an antibiotic regulation, an effective NDA was purely "personal" to the named applicant and was not authority for anyone else to market even an identical product.

(b) *Animal feed.* In 1958 Congress had comprehensively amended the Food, Drug, and Cosmetic Act to control the manufacture and use of substances used in the production and processing of food, including animal feed.[103] The new regulatory provisions were made inapplicable, however, to substances "used in accordance with a sanction or approval granted" pursuant to the Act prior to the effective date of the amendment.[104] Prior sanctions and approvals included, of course, NDA's which had been allowed to become effective.[105]

In accordance with its general policy that an effective NDA was purely "personal" to the applicant, from the beginning the Food and Drug Administration interpreted this "grandfather" provision in the Food Additives Amendment to protect only the applicant himself when the prior sanction or approval relied upon was an effective NDA.[106] By 1962 it was the practice of FDA to confine even the applicant's "grandfathered" status to his use of the precise manufacturing facilities and processes described

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[103] Food Additives Amendment of 1958, 72 Stat. 1784, 21 U.S.C. §§ 321 *et seq.*

[104] Section 2, 72 Stat. 1784, 21 U.S.C. § 321(s)(4).

[105] See H. Rep. No. 1761, 86th Cong., 2d Sess. 87 (HEW explanation of proposed amendments to Food Additives Amendment of 1958).

[106] *Hearings on H.R. 7624 et al. Before the House Comm. on Interstate and Foreign Commerce*, 86th Cong., 2d Sess. 73 (testimony of HEW Secretary Flemming); *id.* at 85 (testimony of FDA Commissioner Larrick).

in the NDA.[107] Yet because FDA was barred by the "Delaney Clause" in the Food Additives Amendment from approving any additive for general use which in experiments could be found to induce cancer,[108] some useful animal feed additives could be produced only by firms with a pre-1958 effective NDA therefor.[109]

To remedy this discrimination, in 1962 the animal feed industry proposed to modify the "Delaney Clause" by allowing useful but carcinogenic substances to be approved as animal feed additives if no residue would remain in edible portions of the animal.[110] The Food and Drug Administration had long supported such a revision.[111] After receiving the endorsement of the House Commerce Committee,[112] the proposal was included in the Drug Amendments of 1962 [113] for the precise purpose of eliminating the discrimination complained of,[114] further confirming the understanding of the 1962 Congress that an effective NDA was purely "personal" to the applicant.

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[107] See, *e.g.*, 108 Cong. Rec. 21080 (Representative Rogers of Florida).

[108] Section 4, 72 Stat. 785, *as amended*, 21 U.S.C. § 348(c)(3)(A). A similar clause had also been included in the Color Additive Amendments of 1960, § 103(b), *as amended*, 21 U.S.C. § 376(b)(5)(B).

[109] See *Hearings on H.R. 7624*, note 106 *supra*.

[110] *Hearings on H.R. 11581*, note 27 *supra*, at 401 (statement of Animal Health Institute).

[111] See *Hearings on H.R. 7624*, note 106 *supra*.

[112] H. Rep. No. 2464, 87th Cong., 2d Sess. 11.

[113] Sections 104(f), -(g), 76 Stat. 785, 21 U.S.C. §§ 348(c)(3)(A), 376(b)(5)(A).

[114] 108 Cong. Rec. 21077-82 (House); *id.* at 22039 (Senate).

C. To Give Effect to Section 107(c)(4) in Accordance With Its Terms, and Thus To Confirm the "Grandfathered" Status of Petitioner's "Me-Too" Products Under the Amended Definition of "New Drug", Would Be Consistent With the Expressed Purposes of This Aspect of the 1962 Amendments and With the Character of the Act's Bifurcated Regulatory Scheme.

1. The 1962 amendment to the statutory definition of "new drug" was not intended to affect drugs already on the market and not being regulated by the Food and Drug Administration as "new drugs", but simply to insure that any new claims for such products would be treated identically with claims for future products not yet on the market.

Virtually the exclusive preoccupation of the sponsors of the 1962 amendments was with the need to subject *future* drugs (and future claims for existing drugs) to pre-marketing scrutiny by FDA for efficacy as well as safety.[115] The legislative history is bereft of any comprehensive statement by the sponsors, or by the Congressional committees which considered the legislation, setting out with precision the extent to which FDA review would be required as to existing claims for drugs already being sold.

Three points, however, emerge with clarity. *First*, the inclusion of "grandfather" provisions in addition to those enacted in 1938 establishes that reliance would continue to be placed solely upon misbranding actions to eliminate false or misleading efficacy claims for at least some post-1938 products already on the market. *Second*, both the Food and Drug Administration and the Congress explicitly noted their unwillingness to require FDA pre-marketing control of existing "old" drugs in the even more critical context

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[115] This is apparent from the emphasis placed throughout on the fact that, under the proposed legislation, FDA scrutiny of efficacy claims would occur *prior* to marketing (*e.g.*, H. Rep. No. 2464, note 27 *supra*, at 3), a concept which could have no relevance to claims already being made for products already on the market.

of safety. *Third,* the single and limited purpose of amending the statutory definition of "new drug"—the amendment whose applicability is in issue here—was simply to assure that future claims for existing products and claims for future products added after their initial marketing, as well as all claims for entirely new products, would be subjected to pre-marketing scrutiny by FDA. There is no evidence whatsoever of any legislative intention to impose "new drug" controls for the first time on existing claims for existing products such as "me-too's" which, as to those claims, were "old drugs" generally recognized as safe.

(a) As first reported by the Senate Judiciary Committee, the bill which ultimately became the Drug Amendments of 1962 [116] made no change whatever in the definition of "new drug", although as originally proposed by Senator Kefauver the bill would have changed the definition to include drugs not generally recognized as effective. The Committee's omission was deliberate.

Some members disagreed directly with the suggestion that new claims for previously approved products should require advance clearance by FDA. As Senator Hruska put it:

> "The change would also cause confusion when a new use is discovered for a safe old drug. For example, if aspirin in its normal dosage were to be newly recommended as efficacious for acne, it should not have to go through the elaborate new-drug procedure. If FDA believes the claim is false, it has ample power to seize the drug as 'misbranded' under existing law." [117]

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[116] S. 1552, 87th Cong., 1st Sess.

[117] 108 Cong. Rec. 10108. Senator Hruska further stated that a change would be "unnecessary to give FDA power to pass on the efficacy of truly new drugs, which are covered by the existing definition because, being new, they are not generally recognized to be safe" (*ibid.*).

Senator Kefauver argued strongly against the movement to delete his proposed amendment of the "new drug" definition. But the sole ground for his objection was that new claims for previously approved products *should* require separate pre-marketing approval by FDA, which ought not to be required to bring its challenges to new claims by way of enforcement actions under the misbranding provisions of the Act.[118]

The formal report of the Senate Judiciary Committee on S. 1552 replied directly to Senator Kefauver's stated objection. Explaining why the proposal to amend the "new drug" definition was unnecessary, the Committee observed that any new claim for a previously approved product *would* in fact require FDA pre-marketing approval, even without a change in the "new drug" definition:

> "any such new use would have to be submitted under a supplemental new drug application and would have to be cleared for safety under existing law, and for safety and effectiveness under the law as it would be amended." [119]

The dissenters from the Committee decision not to amend the "new drug" definition merely reiterated Senator Kefauver's original objection. In their view, it was necessary to expand the definition if the provisions for substantial evidence of efficacy were "to have any real force", but only because

> "otherwise the requirement would only apply to the initial claims made for a drug and not to later claims made after the initial new drug application had been approved." [120]

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[118] 108 Cong. Rec. 10278.

[119] S. Rep. No. 1744 (pt. 1), note 27 *supra*, at 17.

[120] *Id.* at 34 (views of Senators Kefauver *et al.*).

(b) While S. 1552 was pending in the Judiciary Committee, Europe's tragic thalidomide episode received widespread publicity. Attention to this incident increased after S. 1552 was reported, and the White House promptly proposed further amendments to the bill.[121] The Judiciary Committee responded with a supplemental report endorsing the White House proposals. These included expansion of the "new drug" definition to include drugs not generally recognized as effective, as urged by Senator Kefauver. But the sole basis assigned for the change was "to eliminate any possible ambiguity"

> "on the question • • • as to the circumstances and extent to which a new claim or change of claim for effectiveness made after the initial approval of a new-drug application could be made without supporting evidence to be submitted to [FDA] under the new-drug procedure." [122]

On the floor of the Senate, Senator Eastland as Chairman of the Judiciary Committee described the effect of the definitional change in similarly limited terms. The Senator explained that, as a result of the change, "every brand new product, and every *new claim* for an existing product, would be subject to the tests and procedures established" for FDA review of new drug applications.[123] He referred to no other result expected to flow from the change in defi-

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[121] See 108 Cong. Rec. 15692 *et seq.*

[122] S. Rep. No. 1744 (pt. 2), 87th Cong., 2d Sess. 5 (emphasis added). It was with regard to this point that the report noted in the very next sentence that the amended bill would "require • • • all claims for effectiveness, whether made initially in a new-drug application or at any time thereafter", to be approved by FDA prior to marketing.

[123] 108 Cong. Rec. 17366 (emphasis added). See also 108 Cong. Rec. 22050 (statement of Senator Kefauver on supplemental Judiciary Committee report, inserted at his request "to further aid in the understanding of the legislative history", *id.* at 22044).

nition of "new drug". There was no suggestion that FDA approval would have to be obtained as to any existing claims for products already on the market, including "me-too" products, which were then "old drugs" generally recognized as safe. After similarly narrow explanations in the House,[124] the revised S. 1552 was enacted.

(c) As first proposed by Senator Kefauver in April 1961, S. 1552 had contained neither "effective date" nor "grandfather" provisions of any kind. In the House, the principal vehicle for consideration of the Food, Drug, and Cosmetic Act amendments proposed in S. 1552 was the White House-backed H.R. 11581.[125] As introduced in May 1962 by Representative Harris, the Administration bill would have retained the 1938 definition of "new drug" only for "any drug with respect to which an [NDA] was effective" at the time the amendment was enacted, and even then only until such time as approval of the NDA was revoked on any ground, including the new ground of inefficacy or substantial doubt as to efficacy.[126]

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[124] The post-thalidomide report of the House Commerce Committee on the principal House bill (H.R. 11581), which also proposed to amend the definition, echoed the Senate report in stating merely that "this change requires that all claims for effectiveness, whether made initially in a new drug application or at any time thereafter, must be supported by 'substantial evidence' "(H. Rep. No. 2464, note 27 *supra*, at 8). The definitional change was not discussed further; no additional reason for the change was expressed by the committee or its members; and no further anticipated result of the change was ever identified.

[125] 87th Cong., 2d Sess. Hearings (note 129 *infra*) had been held on the House companion to S. 1552 (H.R. 6245, 87th Cong., 1st Sess.) by the House Committee on the Judiciary, to which it had been referred, but the bill was never reported.

[126] Section 108(c). See *Hearings on H.R. 11581*, note 27 *supra*, at 26 (report of Dep't of HEW).

As already noted (p. 54 *supra*), in its July 1962 report on S. 1552 the Senate Judiciary Committee proposed deletion of the amendment to the "new drug" definition.[127] The subsequent White House proposals included not merely reinstatement of such an amendment, but also the limited and temporary "grandfather" provisions of the Harris bill in the House.[128]

Industry witnesses thereafter testifying on H.R. 11581 continued to oppose amendment of the "new drug" definition, on the grounds already endorsed by the Senate Judiciary Committee.[129] It was urged as to the efficacy amendments generally that in any event:

> "There should be a specific provision that the new requirement of 'effectiveness' shall not apply to old drugs already on the market or to new drugs which were cleared before the amendment, and such new drugs should be subject to withdrawal or suspension [of the NDA] only on safety grounds." [130]

One industry witness proposed a "grandfather" clause for the amendment to the "new drug" definition which would parallel the "grandfather" provision in Section 201(p)(1) of the 1938 Act (p. 60 *infra*).[131] The Food and Drug Administration, on the other hand, opposed "a complete

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[127] S. Rep. No. 1744 (pt. 1), note 27 *supra*, at 17.

[128] Amendment No. 4(g)(2), 108 Cong. Rec. 15696.

[129] *E.g., Hearings on H.R. 11581*, note 27 *supra*, at 237-38 (testimony for Pharmaceutical Mfrs. Ass'n), 367-68 (testimony for Proprietary Ass'n). See also *Hearings on H.R. 6245 Before the Antitrust Subcomm. of the House Comm. on the Judiciary*, 87th Cong., 2d Sess., ser. 32, at 450 (statement of Pharmaceutical Mfrs. Ass'n), which preceded the first report of the Senate Judiciary Committee.

[130] *Hearings on H.R. 11581*, note 27 *supra*, at 236 (testimony for Pharmaceutical Mfrs. Ass'n).

[131] *Id.* at 368-69 (testimony for Proprietary Ass'n).

grandfather clause", suggesting merely "a reasonable transition provision." [132]

(d) The second report of the Senate Judiciary Committee, which reinstated the amendment to the "new drug" definition (p. 55 *supra*),[133] adopted neither the across-the-board "grandfather" provisions urged by industry nor the White House/FDA proposal to apply the new definition to existing "old drugs" without significant restriction. The Committee substitute, which was subsequently endorsed by the House [134] and ultimately enacted into law as the "grandfather" provision for the amended definition of "new drug",[135] confers "grandfathered" status on products which at enactment of the amendment met three conditions:

(A) that the drug "was commercially used or sold in the United States";

(B) that the drug was not a "new drug" under the definition then in force, *i.e.*, the original 1938 definition; and

(C) that the drug "was not covered by an effective [new drug] application".[136]

Under this apparent compromise the new definition was made applicable, in furtherance of its purpose, (a) to new

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[132] *Id.* at 573. While this statement was not formally transmitted to the House Commerce Committee until August 30, 1962, it is reasonable to assume that the same position was earlier communicated to the Senate Judiciary Committee during FDA's appearances (see, *e.g.*, 108 Cong. Rec. 14679) at the executive sessions of that Committee to consider the White House proposals for further amendment of S. 1552 as reported (see S. Rep. No. 1744 (pt. 2), note 122 *supra*, at 1).

[133] S. Rep. No. 1744 (pt. 2), note 122 *supra*, at 5.

[134] See H. Rep. No. 2464, note 27 *supra*, at 12.

[135] H. Rep. No. 2526, 87th Cong., 2d Sess. 23 (conference report).

[136] Section 107(c)(4), 76 Stat. 789, 21 U.S.C. note foll. § 321.

claims for existing products and (b) to all claims for future products, whether made in the original NDA or subsequently added. The White House/FDA proposal was partially implemented, but without going beyond the limited reach of that purpose, which had never extended to the imposition of "new drug" controls on existing claims for products such as "me-too's" already being marketed as "old drugs". Thus, the applicability of the amended definition was expanded further, but only to those existing products which were already being regulated or were already required to be regulated under the "new drug" provisions of the 1938 Act, *i.e.*, to products which were still "new drugs" or which, even if no longer "new", were still "covered by an effective [new drug] application".

The Senate Judiciary Committee report accordingly noted that "in the case of a drug on the market which was never subject to the new-drug procedure before, the amendments to the new-drug definition relating to drug effectiveness would not apply to existing labeling claims".[137] The brief comments in the House Commerce Committee report on H.R. 11581 [138] and in the House-Senate conference report [139] precisely echo the Senate report.

(e) Thus, the legislative evolution of neither the "grandfather" provisions of Section 107(c)(4) nor the amended "new drug" definition whose applicability it controls can furnish support for applying the amended definition to pre-1962 "me-too" products for which NDA's had never been filed. We have already shown (pp. 53-56 *supra*) that the Congressional purpose in amending the definition was a clear, narrow and limited one—to insure that "an NDA'd drug would not make new, unsupported claims of

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[137] S. Rep. No. 1744 (pt. 2), note 122 *supra*, at 8.

[138] H. Rep. No. 2464, note 27 *supra*, at 8.

[139] H. Rep. No. 2526, note 135 *supra*, at 23.

efficacy".[140] As this Court long ago stated (*Pacific Mail S.S. Co.* v. *Joliffe*, 2 Wall. 450, 459 (1864)):

> "in construing * * * Acts of amendment * * * it is necessary to observe great caution to avoid giving an effect to these Acts which was never contemplated by the Legislature".

Section 107(c)(4) should not be construed so narrowly that the amendment of the "new drug" definition is given an effect never intended or even contemplated by Congress, and contradicted by its express terms.

2. The government's proposed construction of Section 107(c)(4) would add nothing to what is already provided by the 1938 "grandfather" provision in Section 201(p) itself.

The contrary course now advocated by FDA, particularly when taken together with positions being advanced by the agency on related issues, would render Section 107(c)(4) mere surplusage, adding nothing to the original "grandfather" clause contained since 1938 in the "new drug" definition itself.

The 1938 clause exempts entirely from the "new drug" definition any product which was on the market prior to 1938 so long as it continues to be recommended for the same uses.[141] It is evident from Congress' addition of Section 107(c)(4), therefore, that protection was also in-

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[140] Note, *Drug Efficacy and the 1962 Drug Amendments*, 60 GEO. L.J. 185, 197 n.73 (1971).

[141] "[A] drug not [generally] recognized [as safe and effective for its intended uses] shall not be deemed to be a 'new drug' if at any time prior to enactment of this Act it was subject to the Food and Drug Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; * * *."

Section 201(p)(1), 52 Stat. 1041, *as amended*, 21 U.S.C. § 321(p)(1).

tended to be given to at least some products which had come on the market between 1938 and 1962. The government's reading of Clause (C) of Section 107(c)(4) would nevertheless exclude (1) all products for which a pre-1962 NDA became effective, and (2) all products identical, similar, or related to such an NDA'd product.

This leaves only non-NDA'd post-1938 products which were totally unknown for the pharmaceutical use claimed upon first being introduced. Yet ever since 1938 the term "new drug" has included (a) products without the requisite "general" recognition, and (b) products enjoying such recognition but which have not been used for a material time and to a material extent. *Cf. United States* v. *An Article of Drug* * * * *"Bentex Ulcerine"*, 469 F.2d 875, 880 (5th Cir. 1972).[142]

It would be a contradiction in terms to suggest that a post-1938 drug, which when introduced was unlike any other product already on the market, could then have been

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[142] FDA is presently contending, moreover, that general recognition by qualified experts within the meaning of the statute is impossible in the absence of a body of clinical studies and published literature (compare, *e.g., United States* v. *Forty-One Cases*, 420 F.2d 1126, 1130 (5th Cir. 1970) with *United States* v. *An Article of Drug* * * * *Excedrin P.M.*, CCH FOOD DRUG COSM. L. REP. ¶ 40,486 (E.D.N.Y. 1971). Indeed, the government is presently asking this Court to rule that "there can be no general recognition of safety and effectiveness in the absence of 'substantial evidence' of effectiveness" as defined in the statutory criteria for NDA approval, *i.e.*, "adequate and well controlled investigations, including clinical investigations" (§ 505(d), 76 Stat. 781, 21 U.S.C. § 355(d)). See Memorandum for Respondents, p. 7, *Hynson, Westcott & Dunning, Inc.* v. *Richardson*, No. 72-414, *filed* November 3, 1972, *cert. granted*, 409 U.S. — (1973). While these contentions have been made with reference to "general recognition" under the "new drug" definition of the Act as amended in 1962, at least with regard to drug effectiveness, the standard of "general recognition" dates from 1938 and was not amended or even considered in 1962.

"generally" recognized as safe or "used to a material extent or for a material time" before being marketed.[143] No such product could lawfully have been marketed without an effective NDA, which according to the government would disqualify it for "grandfathered" status. If the government is correct in its over-all view of the 1962 amendments, therefore, Section 107(c)(4) is a nullity serving no function whatever.[144]

To suppose that Congress intended this result would ignore "the basic axiom—that courts should construe all legislative enactments to give them some meaning" (*Rosado* v. *Wyman*, 397 U.S. 397, 415 (1970)). And it is no answer to say that the "purpose" of the 1962 amendments in general so requires. Quite aside from the much more limited purpose of the change in definition of "new drug",[145] and Congress' demonstrated rejection of FDA's proposal to deny "grandfathered" status to all products brought on the market between 1938 and 1962,[146] it is the precise function of *any* "grandfather" clause to limit the applicability of statutory changes made in pursuance of

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[143] Nor is it reasonable to think that any previously unknown product put on the market after 1938 without an effective NDA, and thus in violation of law, would thereafter have been studied in "adequate and well controlled investigations, including clinical investigations", so as to satisfy by 1962 the statutory test as for "old drug" status as construed by FDA (note 142 *supra*). The shortage of qualified clinical investigators has frequently been recognized even by FDA itself. *E.g., Hearings on Present Status of Competition*, note 56 *supra*, at 764, 821 (testimony of FDA Commissioner Goddard).

[144] Nor is it to be supposed that Congress intended to confer "grandfathered" status under Section 107(c)(4) solely upon pre-1962 products which had first come on the market unlawfully, in violation of the criminal prohibition against marketing a "new drug" without an effective NDA (see note 51 *supra*).

[145] See pp. 53-56 *supra*.

[146] See pp. 56-59 *supra*.

some general purpose. As this Court held with reference to the statute of limitations in the Longshoremen and Harbor Workers' Compensation Act (*Pillsbury* v. *United Engineering Co.*, 342 U.S. 197, 200 (1952)):

> "We are aware that this is a humanitarian Act, and that it should be construed liberally to effectuate its purposes; but that does not give us the power to rewrite the statute of limitations at will, and make what was intended to be a limitation no limitation at all".

3. The government's interpretation of Section 107(c)(4) ignores the bifurcated nature of the regulatory scheme created by Congress, and in practical effect would cancel Congress' deliberate choice in 1962 not to require administrative approval by FDA for the continued marketing of all post-1938 drug products, in reliance upon post-marketing civil and criminal misbranding actions as to those post-1938 products which in 1962 were being regulated only as "old drugs".

(a) Contrary to what the government would imply (Resp. Mem., p. 9), Congress did *not* intend in 1962 to require the efficacy of all marketed drugs to be established in administrative proceedings before the Food and Drug Administration. Ever since the original enactment of the statute in 1938 Congress has differentiated between "new drugs" and "old drugs", choosing to regulate the marketing of the latter solely through civil and criminal post-marketing actions for the enforcement of a variety of statutory prohibitions.

Under the 1938 Act the category of "new drug" included only products brought on the market subsequent to enactment of the statute which were "not generally recognized * * * as safe" for their intended uses.[147] The term did not

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[147] Section 201(p), 52 Stat. 1041. The "new drug" provisions of the Act were proposed by, and apparently drafted in, the Food and Drug Administration in the wake of a drug tragedy while the bill was nearing final passage. See *United States* v. *An Article of Drug * * * Bacto-Unidisk*, 394 U.S. 784, 798 (1969) and legislative material there cited.

encompass pre-1938 products no matter what their safety status. The public was protected against unsafe "old drugs" through seizure, injunctive and criminal actions for misbranding, which was defined to prohibit as "misbranded" all drugs dangerous to health when used as directed in the labeling.[148]

This differentiation for regulatory purposes between "new drugs" and "old drugs" was carried forward intact in the 1962 amendments. Administrative control of "new drugs" was expanded to include the requirement that efficacy as well as safety must be proved prior to marketing, and to authorize administrative revocation of marketing authority when efficacy can no longer be established.[149] But the "grandfather" clause in Section 201(p)(1) protecting pre-1938 products was left intact, so that all such products would continue entirely outside the regime of administrative pre-marketing controls without regard to general recognition of either their safety or their effectiveness. And, through Section 107(c)(4), more recently introduced drugs—brought onto the market since 1938 as "old drugs" without having gone through the "new drug" procedure [150] and which in 1962 were still generally recognized as safe—were allowed to remain on the market sub-

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[148] Section 502(j), 52 Stat. 1051, 21 U.S.C. § 352(j). *E.g.*, *United States* v. *Lanpar Co.*, 293 F. Supp. 147 (N.D. Tex. 1968).

[149] Drug Amendments of 1962, §§ 102(b)-(d), 76 Stat. 781-82, 21 U.S.C. §§ 355(b), -(d), -(e).

[150] S. Rep. No. 1744 (pt. 2), note 122 *supra*, at 8; H. Rep. No. 2464, note 27 *supra*, at 8; H. Rep. No. 2526, note 135 *supra*, at 23 (conference report); 108 Cong. Rec. 17366 (Senator Eastland, Chairman of the Judiciary Committee which considered and favorably reported the bill).

ject solely to civil and criminal actions for misbranding to eliminate false or misleading claims of efficacy.[151]

The Senate Judiciary Committee characterized as "ample" the "power" available to FDA through these proven remedies in the case of existing claims for products already on the market and generally recognized as safe, concluding that as to such products nothing more was required.[152] As already shown (pp. 53-56 *supra*), the Committee's subsequent recommendation to amend the definition of "new drug" was intended simply to make clear that *new* claims for "old drugs" or for previously approved "new drugs" would require advance FDA approval, in no way departing from its earlier and continuing position that the misbranding remedies were sufficient as to *existing* claims for "old drugs".

Congress thus evidenced its decision to impose only post-marketing regulation such as this on existing "old drugs" such as "me-too's". Indeed, this choice was further reflected, with the endorsement of the Food and Drug Administration itself, in the even more critical context of safety.

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[151] Section 502(a), 52 Stat. 1050, 21 U.S.C. § 352(a). *E.g.*, *United States* v. *Detroit Vital Foods, Inc.*, 407 F.2d 570 (6th Cir. 1969), *rev'd in part on other grounds sub nom. United States* v. *Kordel*, 397 U.S. 1 (1970). We are advised that nothing in the petition for certiorari in *Hynson, Westcott & Dunning, Inc.* v. *Weinberger* (No. 72-414) was intended to deny that a misbranding action under § 505(a) would lie against such products, despite the government's apparent reading of the petition to the contrary (Memorandum for the Respondents in No. 72-414, pp. 4-5 n.2), and no such suggestion would be well taken. Section 107(c)(4) grants exemption only from the 1962 change in definition of "new drugs", and false or misleading efficacy claims have constituted unlawful "misbranding" since 1938.

[152] S. Rep. No. 1744 (pt. 1), note 27 *supra*, at 17.

S. 1552,[153] the bill which became the Drug Amendments of 1962, would have regulated drug manufacturing and quality control procedures by creating a licensing system for producers of prescription drugs, in which particular establishments would be licensed to produce particular drugs.[154] The testimony of Secretary Ribicoff on S. 1552 denied the necessity for any such system. The Secretary pointed out that the objectives of such a licensing system could be achieved, as to "old" drugs, through an "alternative approach" in which "adulterated" drugs would be defined to include drugs "prepared in inadequate manufacturing facilities, with inadequate personnel, or without adequate control procedures * * * [as] determined by conditions imposed in advance by general regulations."[155]

The mechanism for enforcing compliance with good manufacturing practices as prescribed by regulation, Secretary Ribicoff noted, would be seizure of products produced in violation of the regulations; injunctions against their distribution; and criminal prosecution of the manufacturer involved. The manufacture of "new drugs", on the other hand, would continue to be controlled by requiring the NDA to contain "advance proof" of adequate manufacturing facilities and control procedures.[156]

The licensing system proposed by Senator Kefauver was accordingly rejected, in reliance upon the Secretary's disclaimers.[157] In this way, for purposes of regulating quality control, Congress again deliberately chose to differentiate between "new drugs" and "old drugs", and in the case of "old drugs" to rely upon civil and criminal enforcement

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[153] 87th Cong., 1st Sess.

[154] S. 1552, 87th Cong., 1st Sess., § 4(a)(13).

[155] *Hearings on S. 1552*, note 27 *supra*, at 2591.

[156] *Ibid.*

[157] S. Rep. No. 1744 (pt. 1), note 27 *supra*, at 12; Drug Amendments of 1962, § 101, 76 Stat. 780, 21 U.S.C. § 351(a)(2).

actions rather than pre-marketing approval by FDA in this important area of drug safety.

It would therefore simply obliterate the deliberate distinction drawn by Congress between "new drugs" and "old drugs", and its choice of a separate regulatory mechanism for the latter, to expand the "new drug" provisions of the Act to cover this case. As the Third Circuit noted in rebuffing a similar attempt of the Food and Drug Administration to do so, "other procedures exist within the broad reach of other provisions of the Act which safeguard against" the consequences feared by the agency, in that "misbranding [is] specifically prohibited" (*United States* v. *Kaybel, Inc.*, 430 F.2d 1346, 1347 (1970)).

(b) At bottom, we submit, it is simple dissatisfaction with the clearly expressed intent of Congress which underlies the government's assertion that "me-too" products were "covered" by the effective NDA's governing other manufacturers or other versions of the product. But "neither [this Court] nor the Commissioner may rewrite the statute simply because we may feel that the scheme it creates could be improved upon" (*United States* v. *Calamaro*, 354 U.S. 351, 357 (1957)).

The Food and Drug Administration apparently now believes it would be better, from a regulatory standpoint, if "me-too" products as well as NDA'd products marketed prior to 1962 were subject to the amended definition of "new drug". And so it might seem to some legislators if confronted with the issue.

> "Legislation introducing a new system is at best empirical, and not infrequently administration reveals gaps or inadequacies of one sort or another that may call for amendatory legislation. But it is no warrant for extending a statute that experience may disclose that it should have been made more comprehensive."

Addison v. *Holly Hill Fruit Prods., Inc.*, 322 U.S. 607, 617 (1944).

But the statute which Congress did enact in 1962 preserves the pre-1962 definition of "new drug" for all products which in 1962 were already on the market, were not "new drugs" under that pre-amendment definition, and were not "covered by an effective NDA". There can be no doubt that as understood by Congress this included "me-too" products, by whomever manufactured, including the two manufactured by petitioner.

As the Second Circuit observed with respect to yet another FDA request for a judicial *tour de force* to remedy alleged statutory defects:

> "The case fits perfectly Mr. Justice Brandeis' famous stricture, 'What the Government asks is not a construction of the statute, but, in effect, an enlargement of it by the court, so that what was omitted, presumably by inadvertence, may be included within its scope.'"

Toilet Goods Ass'n. v. *Finch*, 419 F.2d 21, 29 (2d Cir. 1969)).[158] To apply the amended definition of "new drug" to these two products of petitioner would be "to do what the legislative branch of the Government failed to do or elected not to do"—an act of legislation which "is not within * * * [this Court's] province" (*Hanover Bank* v. *Commissioner*, 369 U.S. 672, 688 (1962)).

II. THE COURT OF APPEALS ERRED IN HOLDING THAT, DESPITE THE "GRANDFATHER" PROVISIONS OF THE 1962 AMENDMENTS, THE AMENDED DEFINITION OF "NEW DRUG" APPLIES TO PETITIONER'S FORMERLY NDA'D PRODUCTS WHICH BY 1962 WERE NO LONGER "NEW DRUGS" AND WERE NO LONGER BEING REGULATED AS "NEW DRUGS".

The second category of drugs involved in this case consists of five citrus flavonoid products first marketed by petitioner in 1956 and 1957 under effective NDA's. The district court ruled that these products also enjoy "grand-

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[158] Quoting *Iselin* v. *United States*, 270 U.S. 245, 251 (1926).

fathered" status under Section 107(c)(4). Finding that in 1962 the products were on the market and were no longer "new drugs", thus qualifying under Clauses (A) and (B) of the "grandfather" provisions,[159] the court went on to find that petitioner's actions subsequent to the time the NDA's became effective—endorsed or acquiesced-in by FDA—amounted in practical terms to withdrawal of the NDA's prior to the effective date of the amendments.[160] Thus, the district court concluded, in 1962 the formerly NDA'd products were no longer "covered by an effective application" and the Clause (C) criterion for "grandfathered" status was met.

The court of appeals disagreed. In its view, there had been no provision in the statute for an applicant's "withdrawal" of his NDA once it became effective; the only "withdrawal" contemplated is withdrawal of *approval* by FDA, under the authority of Section 505(e), and here approval had not been withdrawn (A. 469). Thus, the court

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[159] The court of appeals held that "so much the defendants seem to concede" (A. 469), and in this Court the government does not dispute the point (see pp. 23-24 *supra*). There is no question that an NDA'd product can through time become no longer "new", as FDA's own regulations in 1962 recognized (§ 130.9, 25 Fed. Reg. 12595 (1960); see p. 43 *supra*). See *Hearings on Present Status of Competition*, note 56 *supra*, 92d Cong., 2d Sess., pt. 22, at 8530 (HEW Ass't Gen. Counsel Hutt).

[160] See pp. 6-7 *supra*. The district court found (A. 464-65):

> "The plaintiff made that clear through its correspondence with the Federal [sic] Drug Administration. It then ceased compliance with the submittal of data and new labeling, as required by the Federal Drug Administration for products covered by effective NDA's—The record further discloses that the Federal Drug Administration advised the plaintiff in writing that its products covered by [two of the NDA's] were not new drugs—and it was stipulated that the compound in these two products is identical to the bioflavonoid compound in plaintiff's other products and that the recommended uses of all the [bioflavonoid] products are essentially the same".

of appeals concluded, each of these originally-NDA'd products remained "covered by an effective application" on the date of the 1962 amendments.

A. The Statute Has Never Precluded Withdrawal of a New Drug Application by the Applicant as Found To Have Occurred in This Case.

1. The root error of the court of appeals was in confusing withdrawal of the *application,* as found by the district court, with withdrawal of *approval,* as presently authorized by Section 505(e). The court may have been misled by its apparent belief [161] that the acronym "NDA" stands for "New Drug Approval" rather than "New Drug Application". But the belief was mistaken, and in logic the authority of FDA since 1962 to withdraw *approval* of the application has nothing to do with the right of the applicant to withdraw the underlying application itself.

As the government recognizes, moreover, "prior to the 1962 amendments, FDA itself had no authority to withdraw" (Resp. Mem., p. 8). The statute spoke in terms of FDA authority to issue orders "suspending the effectiveness of the application".[162] The *expressio unius* approach relied upon by the court of appeals [163] and by the government [164] to deny petitioner's pre-1962 capacity to withdraw its applications is thus entirely inapplicable here.

2. Nor did the substance of FDA's pre-1962 powers foreclose the capacity of the applicant to withdraw his appli-

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[161] *Bentex Pharmaceuticals, Inc.* v. *Richardson,* 463 F.2d 363, 365 n.2 (4th Cir. 1972), *cert. granted,* 409 U.S. — (1973) (No. 72-555) (A. 259). *Cf. Hynson, Westcott & Dunning, Inc.* v. *Richardson,* 461 F.2d 215, 217 (4th Cir. 1972), *cert. granted,* 409 U.S. — (1973) (Nos. 72-394, 72-414) (A. 173).

[162] Sections 505(e), -(h), 52 Stat. 1053.

[163] A. 469.

[164] Resp. Mem., p. 8.

cation as no longer needed at some time after it had become effective. As the court of appeals recognized in upholding the jurisdiction of the district court to entertain this action, FDA has always been wholly without authority to consider or decide in Section 505(e) proceedings whether a previously-NDA'd product continues to be a "new drug", and that issue could never have been raised by either party to a Section 505(e) proceeding.[165] Section 505(e) could never have been invoked by petitioner, moreover, and not even by FDA to terminate NDA "coverage" on the ground that the product had become "generally recognized as safe" and therefore no longer required the regulatory controls imposed on NDA'd products. Section 505(e) has always been a provision of limited scope, permitting the Food and Drug Administration to move against an NDA only for the very opposite substantive reason—that the evidence no longer shows the product to be safe (or, under the amended statute, effective) and hence no longer allows the product to be marketed.

3. To use the recent words of counsel for the Food and Drug Administration, pre-1962 NDA's are "obsolete or inactive" when "the drug has become an old drug".[166] Common sense says that an effective NDA which thus became superfluous may and should have been retired on that ground. Because the statute prescribed no particular procedure for doing so, one must be inferred from the whole scheme and purpose of the Act "if it is to be treated as a working instrument of government and not merely as

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[165] The government currently attacks that ruling in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72-555, and defends the contrary view of the Third Circuit in *CIBA Corp.* v. *Weinberger*, No. 72-528. The government's position is also supported by the petitioner in *Hynson, Westcott & Dunning, Inc.* v. *Weinberger*, No. 72-414.

[166] *Hearings on Present Status of Competition*, note 56 *supra*, 92d Cong., 2d Sess., pt. 22, at 8530 (HEW Ass't Gen. Counsel Hutt).

a collection of English words" *United States* v. *Dotterweich*, 320 U.S. 277, 280 (1943)). And it strains both common sense and reason for the government now to deny that a pre-1962 NDA became "obsolete or inactive" when the "old drug" status of a product was asserted by the manufacturer, ratified by FDA, acted upon by the manufacturer (in discontinuing supplemental NDA's), and acquiesced-in by the agency (in no longer imposing NDA controls).

B. Regardless of Whether Petitioner Could Lawfully Have "Withdrawn" Its Applications After They Became Effective, Under the Facts as Found by the District Court, Its Formerly NDA'd Products Were No Longer Covered by an Effective NDA in 1962.

In any event, the court of appeals' preoccupation with whether petitioner had the "right" to "withdraw" its NDA's misconceived the critical inquiry. Regardless of how the district court had formulated the issue, the question on appeal was not whether petitioner had withdrawn its NDA's, or indeed even whether petitioner had a "right" to "withdraw". Properly stated, the true question was whether petitioner's bioflavonoid products which had earlier been NDA'd were, on October 9, 1962, still "covered by an effective [new drug] application".

Even prior to 1962, the function of the NDA was not exhausted when the application became effective. An effective NDA was considered by the Food and Drug Administration to be "an official legal document" which "defines in no uncertain terms the indications, contraindications, cautions, dosage and basic professional literature", "to break the terms of [which] is to court trouble".[167] Accordingly, manufacturers of drugs covered by effective NDA's

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[167] Holland, *Current Drug Problems Under the Federal Food, Drug, and Cosmetic Act*, 11 FOOD DRUG COSM. L.J. 486, 489 (September 1956). The cited author was then Medical Director of FDA.

were obligated by the regulations then in force [168] to report all changes in the composition, manufacturing facilities or processes, quality controls, and labeling of such products and to obtain advance approval from the Food and Drug Administration if the change would be significant.

The purpose of this reporting and approval requirement was to enable FDA to continue its regulatory function after an NDA became effective. As the Deputy Commissioner of Food and Drugs stated in 1955:

> "Evaluation of [safety] evidence does not end with the initial marketing of the drug. Up to this point, it has been produced in small quantities and restricted to the use of investigators qualified to perform the scientific testing necessary to establish its safety. Experience in widespread use may require label changes, and mass production may result in improvement of manufacturing facilities." [169]

The district court relied upon the sequence of events between the time petitioner's NDA's became effective and the date of the 1962 amendments for its finding of practical and effective withdrawal of the NDA's prior to October 9, 1962, and on this basis concluded that thereafter petitioner's formerly NDA'd products were no longer "covered". In its preoccupation with the abstract question whether petitioner lawfully could "withdraw" its NDA, the court below ignored the underlying facts on which the district court relied, which showed that by 1962 the products involved were no longer being treated by either the manufacturer or FDA as subject to the continuing regulatory controls applicable to NDA'd products. These facts, we submit, surely justified the district court's ultimate conclusion that on October 9, 1962, the products were no longer "covered" by an effective NDA.

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[168] Section 130.9, 25 Fed. Reg. 12595 (1960).

[169] Harvey, *Administration of the Food, Drug, and Cosmetic Act*, 10 Food Drug Cosm. L.J. 441, 446 (July 1955).

However characterized, the nub of what happened here was that through the actions of both petitioner and FDA, taken together, the NDA's were inactivated and by 1962, despite their former status, the products involved had become no longer "covered by an effective [new drug] application" within the meaning of Clause (C) of Section 107(c)(4). Had Congress intended to apply the amended definition of "new drug" to products such as these, it would have conferred "grandfathered" status only where the drug "was not a new drug" under the 1938 Act and "*had never been* covered by an effective application". But Congress in fact legislated differently, and as the district court held, the "grandfather" provisions which it did enact embrace petitioner's formerly NDA'd but no longer "new" and no longer "covered" products.[170]

C. To Apply Section 107(c)(4) to Petitioner's Formerly NDA'd Products Would Be Consistent With the Purpose of the 1962 Amendment to the "New Drug" Definition and Would Not Make Surplusage of Any Portion of the Statute.

We have already shown that Congress' purpose in amending the definition of "new drug" was solely to insure FDA pre-marketing scrutiny of (1) future claims for existing products and (2) claims first made for future products subsequent to approval of the original NDA (pp. 53-56 *supra*). There is no evidence, as we have seen, that Congress intended to impose "new drug" controls on existing claims for products already on the market which were not then being regulated as "new drugs".

There can accordingly be no warrant in the purposes of the amendments for failing to recognize the "grandfathered" status conferred upon petitioner's formerly NDA'd but no longer "new" products under Section

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[170] Because the court of appeals relied upon these NDA's to deny "grandfathered" status to petitioner's "me-too" products, reinstatement of the district court's holding on this point would *a fortiori* require reversal as to the "me-too" products as well.

107(c)(4). Indeed, the Food and Drug Administration itself so interpreted Section 107(c)(4) immediately after its enactment, and only subsequently decided upon its present contrary position.[171] As FDA thus originally recognized, the remedy for allegedly false or misleading efficacy claims for such formerly NDA'd products is a misbranding action, as contemplated by Congress, in the same manner as all other "old drugs" under Congress' bifurcated regulatory scheme.

It is true that, as the court of appeals stressed (A. 470), the only specific reference in the legislative history of Section 107(c)(4) is to products "that have never been subject to the new-drug procedure". But there is nothing to suggest that this and similar comments were intended comprehensively to catalogue or exhaust the circumstances in which Section 107(c)(4) would be applicable, or that the authors had in mind that precise group of pre-1962 products, such as petitioner's, which had once been subject to "new drug" procedures but which had then become no longer "new" and which, additionally, had ceased to be regulated as "new drugs" by FDA.[172]

Nor does this conclusion make "surplusage" of Clause (C), as the court below feared (A. 469). It is not our position that the fact that an NDA'd product had become

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[171] Notes 63-64 *supra*.

[172] The two-year freeze imposed by Section 107(c)(3), which temporarily barred proceedings under the amended § 505(e) to revoke approval of effective pre-1962 NDA's so as to allow the applicants thereunder to compile their evidence, serves an entirely different function from Section 107(c)(4). The two-year provision was intended to apply to "a new drug already on the market" (S. Rep. No. 1744 (pt. 2), note 122 *supra*, at 8; 108 Cong. Rec. 22039 (Senator Kefauver explaining House-Senate conference report); *cf.* H. Rep. No. 2464, note 27 *supra*, at 12), whereas Section 107(c)(4) deals with products which in 1962 were not "new drugs".

generally recognized as safe and no longer "new", standing alone, automatically inactivated the NDA. We assume *arguendo* that there must be some further action which removes the product from new-drug regulation, before it can be found the product is no longer "covered" by an effective NDA.

Here, however, FDA had not only ruled that the products were generally recognized as safe, and thus "not new", but the agency had unambiguously acquiesced in petitioner's withdrawal of these products from "new drug" regulatory procedures. FDA's own actions in connection with those of petitioner established that the products were no longer "covered." According to the district court, it was necessary for petitioner to show these additional facts in order to satisfy the criterion for exemption prescribed by Clause (C). Under no view of the statute as interpreted and applied by the district court, therefore, can Clause (C) be considered surplusage.

CONCLUSION

The judgment of the court of appeals should be reversed as to each of petitioner's citrus flavonoid products, both formerly NDA'd and "me-too", for the reasons stated in Point II above (pp. 68-76). As to petitioner's "me-too" products, Bivam and Duo-CVP with Vitamin K Capsules, the judgment should be reversed for the addditional and wholly separate reasons stated in Point I (pp. 21-68).[173]

Respectfully submitted,

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March 1, 1973

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[173] On the ground that "there are now no longer any disputed issues of fact in the present case", the government has abandoned its thus-far-unsuccessful challenge to the district court's exercise of jurisdiction to hear and decide this case on the merits (Resp. Mem., p. 6 n.9). However, if this Court were to hold in *CIBA Corp.* v. *Weinberger* (No. 72-528) that the government is correct in its view that, in cases such as this, "the primary jurisdiction doctrine may oblige courts to defer to FDA" (*ibid.*), then the appropriate disposition of this case might be to vacate the judgment of the court of appeals, and to remand to the district court with directions to dismiss without reaching the merits, so as to allow petitioner to contest *de novo* the alleged "new drug" status of its citrus flavonoid products in the still-pending NDA approval revocation proceeding. For if the Court were generally to require primary adjudication of "new drug" status before FDA, it would seem illogical, if not impermissible under the statutory scheme as thus construed, to apply a different rule in the present case merely because the issue has already been adjudicated in the district court without benefit of an FDA determination on the record.

APPENDIX

APPENDIX

Section 505 of the Federal Food, Drug, and Cosmetic Act of 1938, 52 Stat. 1052, as originally enacted and in force until October 10, 1962, provided in pertinent part:

(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such person shall submit to the Secretary as a part of the application

(1) full reports of investigations which have been made to show whether or not such drug is safe for use;

(2) a full list of the articles used as components of such drug;

(3) a full statement of the composition of such drug;

(4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

(5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and

(6) specimens of the labeling proposed to be used for such drug.

(c) An application provided for in subsection (b) shall become effective on the sixtieth day after the filing thereof unless prior to such day the Secretary by notice to the applicant in writing postpones the effective date

of the application to such time (not more than one hundred and eighty days after the filing thereof) as the Secretary deems necessary to enable him to study and investigate the application.

(d) If the Secretary finds, after due notice to the applicant and giving him an opportunity for a hearing, that

(1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;

(2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions;

(3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; or

(4) upon the basis of the information submitted to him as part of the application or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions, he shall, prior to the effective date of the application, issue an order refusing to permit the application to become effective.

(e) The effectiveness of an application with respect to any drug shall, after due notice and opportunity for hearing to the applicant, by order of the Secretary be suspended if the Secretary finds

(1) that clinical experience, tests by new methods, or tests by methods not deemed reasonably applicable when such application became effective show that such drug is unsafe for use under the conditions of use upon the basis of which the application became effective, or

(2) that the application contains any untrue statement of a material fact. The order shall state the findings upon which it is based.

(g) Orders of the Secretary issued under this section shall be served

(1) in person by any officer or employee of the department designated by the Secretary or

(2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) An appeal may be taken by the applicant from an order of the Secretary refusing to permit the application to become effective, or suspending the effectiveness of the application. Such appeal shall be taken by filing in the district court of the United States within any district wherein such applicant resides or has his principal place of business, or in the District Court of the United States for the District of Columbia, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. • • •

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"GRANDFATHER CLAUSE" IN 1962 DRUG LAW COVERS: ALL DRUG PRODUCTS MARKETED ON OCT. 9 THAT WERE NOT SUBJECT, AT THAT TIME, TO AN ACTIVE NDA: FDA RULES

The "Grandfather Clause" in the 1962 drug law applies to every drug product marketed in the U.S. on Oct. 9, 1962 that was not covered at the time by an "active" New Drug Application (NDA).

Two groups of drug products are "grandfathered": (1) Those which never had an NDA; and (2) Those which were cleared through the NDA procedure but were subsequently transferred from "new drug" status by a letter from FDA.

This ruling, stated definitely and precisely by Deputy FDA Com. Harvey, clarified one of the most important and controversial questions that confronted both industry and govt. as a result of an apparent conflict between the language of the 1962 drug law and its legislative history.

Harvey stated the Food & Drug Administration's (FDA) interpretation in one sentence -- almost paranthetically -- in his recent speech before the Drug & Allied Product Guild (see quotation in box below). Expanding on the key half-sentence in his speech, he told "The Pink Sheet" that FDA believes the "Grandfather Clause" applies to every marketed drug product, not covered by an NDA, at a particular time -- Oct. 9, 1962.

**"GRANDFATHER CLAUSE"
1962 Drug Law
DEPUTY FDA COM. HARVEY:**

In the future, mfrs. of "new drugs" will therefore need to demonstrate their effectiveness....

There is a 2-year transitional period for drugs now having an effective new drug application before this requirement becomes effective, and drugs not now requiring a new drug application because of safety will not become new drugs under the effectiveness concept if claims and representations remain as they were at the time of the statute's enactment. This is the so-called "Grandfather Clause."

Language in the legislative history might have formed the basis for an FDA view that the "Grandfather Clause" covered only those drug products -- on the market Oct. 9 -- which had never been cleared through the NDA procedure.

The second Senate Judiciary Cmte. report on the bill said that: "Drugs which are commercially used at the time of enactment and which were never subject to the 'new drug' procedure before, shall not be considered 'new drugs' by reason of the new 'effectiveness' requirements added.... by the bill."

House Interstate Cmte.'s report also had a comparable statement. Had this legislative history been translated into the regulatory system, every drug product which had been NDA-ed since 1938 could have been placed under the NDA procedure again for the purpose of requiring substantial evidence to prove

its effectiveness. To remain under the protection of the "Grandfather Clause," a drug product must be sold only for the conditions prescribed, recommended or suggested in the labeling on Oct. 9.

A strong body of opinion at the FDA staff level favored the legislative history interpretation of the "Grandfather Clause." They wanted the effectiveness provision of the "new drug" section to cover as many products as possible. In short, they wanted the clause to cover the fewest number of products.

When the issue finally arrived at FDA's topside, practical considerations as well as legal interpretation pointed to the ruling that was adopted. FDA didn't want to discriminate between pioneer products that had been cleared through the NDA procedure and their follow-up products that had been marketed after the time when the pioneers were shifted from "new drug" to "old drug" status.

Some of the early cortical steroids, for example, were marketed after NDA clearance, but later were declared to be "old drugs" and many different brands were sold without going through the NDA procedure.

Another practical guide emerges from this line of FDA thinking. If a mfr. wants to market a new product today that is identical with a grandfathered product which was on the market Oct. 9, he probably will not have to process the new competitive product through the NDA procedure.

But he will have to check in with FDA to make certain that his new product is actually protected by the "Grandfather Clause." The checking in procedure could involve almost as much information as FDA required for clearance of "new drugs" under the NDA procedure a few years ago.

FDA Won't Ignore Effectiveness During Two-Year Grace Period For NDA-ed Products

Drug products marketed on last Oct. 9 and still subject to NDA coverage cannot be challenged directly under the effectiveness standard until Oct. 10, 1964. The law provided a two year grace period, but in the day-to-day operation of the NDA procedure, this may not mean very much.

The new law provides that FDA can move for the withdrawal of an NDA whenever it gets new evidence questioning the safety or effectiveness of a product. In strict legal terms, the withdrawal procedure shifts a burden of proof to the govt.

But FDA has seldom had to resort to formal legal procedures in administering the NDA system. In the past, operating mechanisms have been worked out to achieve a regulatory approach, and industry has at least acquiesced.

Whenever an NDA supplement raises an issue close to effectiveness, or even directs attention to a question of effectiveness, FDA can be expected to bring the matter up with the mfr. without waiting until Oct. 10, 1964.

FDA-ers feel they can get into trouble either way: If they hew strictly to the two-year grace period, they could be criticized, even by mfrs., for keeping mum on effectiveness questions when passing NDA supplements on corrolary matters. On the other hand they know they also can get in trouble by pressing effectiveness too hard or too far on existing products before Oct. 10, 1964. In an exchange of correspondence with PMA General Counsel John Worley, Deputy FDA Com. Harvey had promised there would be no "delay in handling acceptable supplements" to NDAs.

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FDA'S FEB. 15 CONFERENCE ON NEW LAW SHOWS DISAGREEMENT BETWEEN DEPUTY COM. HARVEY & GENERAL COUNSEL GOODRICH ON COVERAGE OF THE "GRANDFATHER CLAUSE"

A disagreement among FDA topsiders over the meaning of the important "Grandfather Clause" in the 1962 drug law, which became apparent during the Q-&-A at the Feb. 15 "open conference," spotlighted the fluid state of govt. thinking in many areas of the new regulatory system, now being worked out.

Deputy FDA Com. Harvey, in a speech delivered Jan. 24, flatly declared that any drug product which did not have an "active" New Drug Application (NDA), as of Oct. 9, 1962, was protected by the "Grandfather Clause" from a requirement that the mfr. produce substantial data in support of its effectiveness -- providing no change is made in the product or its claims.

"GRANDFATHER CLAUSE"
1962 Drug Law
FDA COUNSEL GOODRICH

By a "grandfather clause," it means that the status of the drug on the date of the enactment is not changed by the enactment. The basic grandfather clause is that none of these requirements apply to a new drug which is generally recognized as both safe and effective.

For old drugs which are not generally recognized as safe, if they were on the market with never any clearance through the new drug procedures, they are permanently protected to use unsubstantiated claims, provided these claims are not changed.

The third phase of it is for a drug which was once cleared through the new drug procedures on an issue of safety alone, this is protected for two years in order to allow the sponsor to accumulate a scientific basis for making his claims.

This view was confirmed in an interview with Harvey, and was reported in the Feb. 4 issue of "The Pink Sheet." The same interpretation was repeated by Earl L. Meyers, New Drug chief chemist, in a comprehensive speech on the new law, delivered Feb. 8.

(EDITORS' NOTE: The quotation from Harvey's Jan. 24 speech, appearing in the box on the next page, is reprinted from the Feb. 4 issue of "The Pink Sheet.")

W. W. Goodrich, FDA's general counsel, however, took another view on the "Grandfather Clause" when he answered a series of questions at the Feb. 15 "open conference."

In the presence of an SRO audience -- about 750 -- he disagreed with Harvey's earlier interpretation, and gave the opinion that the "Grandfather Clause in effect, gives full protection only to drug products that have never been cleared through the NDA procedure.

(EDITORS' NOTE: See box at the left for full text of one of Goodrich's several answers to the same question. All of them were consistent.)

After the "open conference," Harvey acknowledged to "The Pink Sheet" that there was a difference in views on the question between Goodrich and himself. The deputy commissioner said this indicates FDA's final view is not firmed up yet and will have to be thrashed out.

S-2

[Continuation of story omitted]

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SUPREME COURT, U.S.
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MICHAEL RODAK, JR., CLERK

IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

Nos. 72-394, 72-414, 72-528, 72-555 and 72-666

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs, *Petitioners and Respondents,*

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, *Respondent and Cross-Petitioner.*

CIBA CORPORATION, *Petitioner,*

v.

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs

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CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs, *Petitioners,*

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

USV PHARMACEUTICAL CORPORATION, *Petitioner,*

v.

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

Nos. 72-394 and 72-414

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners and Respondents,

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED,

Respondent and Cross-Petitioner.

No. 72-528

CIBA CORPORATION,
a corporation of the State of Delaware,

Petitioner,

v.

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs

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No. 72-555

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners,

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

No. 72-666

USV PHARMACEUTICAL CORPORATION,
Petitioner,
v.
CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs

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MOTION FOR LEAVE TO FILE BRIEF AMICI CURIAE IN SUPPORT OF THE UNITED STATES ON BEHALF OF THE AMERICAN PUBLIC HEALTH ASSOCIATION, THE NATIONAL COUNCIL OF SENIOR CITIZENS, AND CONSUMERS UNION OF UNITED STATES, INC.

The American Public Health Association, National Council of Senior Citizens, and Consumers Union of United States, Inc., hereby respectfully move for leave to file the attached brief *amici curiae* in support of the United States in these cases. The consent of the United States has been obtained and has been filed with the Clerk of this Court. The consent of all the pharmaceutical manufacturers was not obtained.

The American Public Health Association and National Council of Senior Citizens were previously granted permission to file a brief *amici curiae* in support of the Government's petition for certiorari in one of these cases, *Richardson* v. *Hynson, Westcott and Dunning*, No. 72-394.

The interest of these two *amici* in these cases arises in part from their recent successful court action in United States District Court for the District of Columbia against

the Food and Drug Administration, *American Public Health Association* v. *Veneman*, C.A. No. 1847-70 (August 23, 1972). The 1962 Amendments to the Food, Drug and Cosmetic Act of 1938 require the Food and Drug Administration (FDA) to withdraw from the market drugs first introduced between 1938 and 1962 for which there is no "substantial evidence" of effectiveness. FDA did not begin to act to implement this mandate for nearly a decade, and thousands of ineffective drugs are still being sold. The District Court in *Veneman* found that FDA had in effect "stayed" implementation of the Act and directed FDA to proceed "expeditiously" to withdraw ineffective drugs from the market, pursuant to a court-established timetable.

In the attached brief, *amici* demonstrate that the decisions of the Court of Appeals for the Fourth Circuit in three of the four cases now before this Court would, if sustained, as a practical matter block compliance by FDA with the order of the District Court in *American Public Health Association* v. *Veneman*. *Amici* seek to file a brief supporting the United States in order to protect the interest of the public in enforcement of this extremely important statute, as interpreted in the *Veneman* case.

In the brief, *amici* do not seek to reiterate the legal arguments of the parties in each case, but to identify several major issues crucial to enforcement of the 1938 Act that are raised by the cases taken together, and to show some of the practical ramifications of these issues.

All three *amici* have had a long-standing concern for protecting the public from the abuses of ineffective drugs. The American Public Health Association is a national professional organization whose membership of over 26,000 consists primarily of professional public health workers, including doctors, nurses, and hospital administrators. The Association, which was 100 years old last year, was

organized to provide public health professionals with a vehicle for influencing national and local public health policy. It publishes a monthly magazine, the *American Journal of Public Health*, consisting of papers from its membership, and a monthly newspaper, *The Nation's Health*. Concern with this country's drug problem, including drug ineffectiveness, dominated a major part of the 1972 annual meeting of the Association. As a result, several resolutions were adopted supporting broader regulation of the drug industry and increased appropriations to FDA and other federal agencies charged with the responsibility of safeguarding the public's health.

The National Council of Senior Citizens, formed in 1961, is a non-profit association of over 3,000 senior citizen groups from different states with a combined membership of over 3,000,000 elderly people. The purpose of the organization is to provide education and to act as a national clearinghouse on matters of interest to senior citizens. The interest of the elderly in drug effectiveness is a critical one. Of people 65 and older, over 85 percent are suffering from one or more chronic conditions and, as a result, elderly people use three times the amount of drugs as the average American citizen. This need for drugs—coupled with the fact that one out of four of the 22 million persons under the poverty line of $1,900 a year is over the age of 65—makes the problem of costly and ineffective drugs an extremely important matter for senior citizens. In view of the importance of drugs to the elderly, the Council has actively participated in drafting legislation to extend Medicare coverage to out-of-hospital drugs, and joined with two other organizations in 1966 to form a drug cooperative in an effort to reduce the rising cost of drugs.

Consumers Union of United States, Inc., with approximately 350,000 members, is the largest consumer organization in the United States. It was organized in 1936

as a non-profit corporation under the laws of New York to provide information and counsel to consumers concerning goods and services. Consumers Union engages in extensive testing of products and publishes test results and general consumer information in its monthly magazine, *Consumer Reports*, which has a paid circulation of approximately 2.2 million readers. On behalf of its members, Consumers Union takes public positions on many significant issues of importance to consumers and advances those positions before administrative agencies and the courts.

In numerous articles over the years, *Consumer Reports* has informed its members about activities of FDA with respect to the safety and efficacy of drugs. Consumers Union has published a book on the safety and efficacy of over-the-counter drugs, entitled *The Medicine Show*. In December, 1972, Consumers Union brought an action in the United States District Court for the District of Columbia to compel FDA to implement its earlier final order withdrawing marketing approval for a drug that failed to meet the efficacy requirement of the 1962 Amendments. *Consumers Union* v. *Richardson, et al.*, C.A. No. 2498-72.

The filing of the brief *amici curiae* is timely. Petitioners' briefs in these cases were required to be filed by March 1, 1973, and all respondents' briefs (including those of the United States in *Ciba*, *USV*, and *Hynson*, No. 72-414) thirty days later. By permission of the Clerk of the Court, since the *amici* brief is a consolidated brief covering all the cases, *amici* were permitted to file their brief pursuant to the time schedule established for the United States as respondent. In fact, printed briefs in *USV* and *Bentex* and the brief of the United States as Petitioner in *Hynson*, No. 72-394, were not filed until the week following March 1, 1973. Since Petitioner USV filed a typed copy of its brief on March 1, *amici* were requested by the Clerk to file ten typewritten copies of

their brief on or by March 31 and to file the requisite number of printed copies immediately thereafter.

CONCLUSION

For the foregoing reasons, we respectfully submit that the Motion to File Brief *Amici Curiae* in Support of the United States should be granted.

Respectfully submitted,

/s/ Bruce J. Terris
BRUCE J. TERRIS

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Attorneys for Consumers Union of United States, Inc.

IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

Nos. 72-394 and 72-414

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners and Respondents,

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED,

Respondent and Cross-Petitioner.

No. 72-528

CIBA CORPORATION,
a corporation of the State of Delaware,

Petitioner,

v.

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs

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No. 72-555

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners,

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

No. 72-666

USV PHARMACEUTICAL CORPORATION,
Petitioner,

v.

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs.

BRIEF AS AMICI CURIAE IN SUPPORT OF THE UNITED STATES ON BEHALF OF THE AMERICAN PUBLIC HEALTH ASSOCIATION, THE NATIONAL COUNCIL OF SENIOR CITIZENS, AND CONSUMERS UNION OF UNITED STATES, INC.

STATEMENT OF INTEREST OF AMICI CURIAE

The interest of *amici curiae* is fully described in the Motion for Leave to File Brief Amici Curiae above.

INTRODUCTION

In the Food, Drug and Cosmetic Act of 1938, as amended in 1962, Congress provided that all drugs sold to the American public shall be both safe and effective for their intended uses. But, for reasons we develop in this brief, the Congressional mandate embodied in the Act has never been carried out with respect to *ineffective* drugs whose withdrawal from the market was required by the 1962 Amendments.

It was not until 1969 and 1970 that the Food and Drug Administration [hereinafter FDA] began to adopt procedures and initiate actions essential to vigorous en-

forcement of the Act and protection of the American consumer. The overriding issue before the Court in these four cases is whether FDA's belated but salutary efforts to implement this Act will be stymied and the clear Congressional intent to remove ineffective drugs from the market permanently thwarted.

In this brief, *amici* do not reiterate all the legal arguments supporting FDA's enforcement program, which are exhaustively reviewed in the briefs for the United States. FDA's program is totally consistent with the statutory scheme and is designed to afford maximum fairness to drug producers and the most effective protection to consumers. Most courts that have recently considered aspects of FDA's regulatory approach have sustained and commended it,[1] and one District Court, in an action brought by two of *amici curiae*, has even held that it is not proceeding fast enough.[2]

Rather, *amici* seek to (1) identify from the mass of material surrounding these cases the three distinct legal issues that are posed, and (2) demonstrate why, as a practical matter, acceptance by this Court of the restricted and distorted view of the Act pressed by the drug manufacturers would bring FDA's encouraging new efforts to implement the Act to a halt.

Accordingly, this brief treats the four cases in a coordinated fashion and discusses at some length matters not fully explored in the briefs of the parties, including

[1] See Upjohn Co. v. Finch, 422 F.2d 944 (CA 6, 1970); Pfizer, Inc. v. Richardson, 434 F.2d 536 (CA 2, 1970); Ciba-Geigy Corp. v. Richardson, 446 F.2d 466 (CA 2, 1971); American Cyanamid Co. v. Richardson, 456 F.2d 509 (CA 1, order of one judge denying stay); Pharmaceutical Manufacturers Association v. Richardson, 318 F. Supp. 301 (D. Del. 1970).

[2] American Public Health Association v. Veneman, CA No. 1847-70 (D.D.C. Aug. 23 and Oct. 11, 1972), discussed at page 16, *infra*.

the importance of the effectiveness requirement, the dimensions of the enforcement problem with respect to both prescription and over-the-counter drugs, and the practical ramifications of a decision adverse to FDA.

The drug manufacturing industry originally opposed adoption of the provisions enacted in 1962, which require withdrawal of ineffective drugs from the market, on the ground that such measures were unnecessary, and it has fought their effective enforcement since 1962.[3] Its briefs in these cases are conspicuously devoid of any reference to the important goals Congress sought to achieve by this legislation. The reason for this is that the legal positions the industry espouses are fundamentally inconsistent with the Congressional purpose. These cases represent the final chapter in the drug manufacturers' efforts to undo in the courts what they were unable to prevent Congress from doing in 1962.

This Court need not and should not read the Act to disable the expert administrative agency charged with attaining its important public health and consumer goals from doing so. Rather, the Court should construe the Act in harmony with the purposes for which it was enacted.

This brief will:

I. Describe, by summarizing the operation of the Act and its enforcement by FDA, how meaningful enforcement of the 1962 Amendments has been delayed for over a decade;

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[3] See Jurow, The Effect on the Pharmaceutical Industry of the "Effectiveness" Provisions of the 1962 Drug Amendments, 19 Food Drug Cosm. L.J. 110 (1964); Mintz, FDA and Panalba, A Conflict of Commercial, Therapeutic Goals?, 165 Science 875 (1969). Commissioner Ley, in 1969, characterized the industry's resistance to the 1962 Amendments as "intense and prolonged." Hearings on Drug Efficacy Before a Subcomm. of the House Comm. on Government Operations, 91st Cong., 1st Sess., pt. II, at 238.

II. Summarize, for the Court's convenience, the three distinct but interrelated legal issues crucial to continued enforcement of the Act that are presented by the four cases before it;

III. Demonstrate that the position urged by the drug manufacturers on each of these three issues would, as a practical matter, block FDA's enforcement of the Act and indefinitely thwart the Congressional mandate that ineffective drugs be removed from the market; and

IV. Show briefly, with respect to each issue, that FDA's regulatory program is fully consistent with the statutory language and history, as well as the purposes of the Act.

I. THE 1962 AMENDMENTS, WHICH ARE ONLY NOW BEGINNING TO BE ENFORCED, ARE AN IMPORTANT PROTECTION FOR CONSUMERS.

In 1938 Congress, in the wake of a major drug tragedy, first provided for pre-marketing administrative clearance of pharmaceuticals sold in interstate commerce, to assure the public that such drugs would be safe for their recommended uses. Federal Food, Drug and Cosmetic Act, 52 Stat. 1040. The pre-marketing clearance scheme did not apply to every drug brought on the market after 1938, but only to those drugs not already "generally recognized" by qualified experts as "safe." Drugs not so recognized were defined by the Act as "new drugs". The clearance scheme established by the 1938 Act was in large part self-policing. The manufacturer itself was required to determine whether a drug was a "new drug" within the meaning of the Act, and if so, to submit a "new drug application" [hereinafter NDA] to the FDA setting out scientific evidence of the drug's safety. The NDA automatically became effective, and the manufacturer could then market its drug unless, within a specified period of

time, FDA (after notice and opportunity for hearing) decided that the evidence did not establish the drug's safety, and disapproved the application.[4] (NDA's could also be later withdrawn by FDA on the same grounds.) The self-policing aspect of the scheme was, however, supplemented by powerful incentives to manufacturers to seek clearance in doubtful cases. The Act gave FDA power to seek an injunction in District Court against distribution of non-NDA'd "new drugs" and to seize such drugs in condemnation and libel proceedings. Marketing of a "new drug" without an effective NDA could also be made the basis for a criminal prosecution.

The large volume of NDA's received by FDA relative to its comparatively small staff and the paramount need to protect the public from potential hazards of brand new drug ingredients gave rise to an administrative anomaly that has become central to resolution of these four cases: the "me-too" problem. When one manufacturer obtained an effective NDA for a "new drug" containing some new compound or active ingredient not theretofore generally recognized as safe, other manufacturers often rushed to produce and market the identical or a substantially similar drug containing the same ingredient, but under a different trade name or under the generic name. On occasion, a manufacturer would even market copies of its own drug. Sometimes manufacturers filed independent NDA's on these copies or so-called "me-too" drugs. More often they did not, apparently taking the position that because the pioneer drug was already being marketed under an effective NDA, its basic ingredient had been demonstrated to FDA to be "safe", and the copy therefore did not require an NDA. Some manufacturers re-

[4] The 1938 Act provided that orders denying or suspending an NDA were reviewable on the administrative record in the District Courts. The 1962 Amendments provided for direct review of such orders in the Court of Appeals. § 505(h), 21 U.S.C. § 355(h).

quested advisory opinions from FDA on these "me-too" drugs and, in some cases, received opinions that no NDA was required to be filed.

The dimensions of this problem were considerable. The 1940's and 1950's were the heyday of prescription drug development, and it is estimated that for every NDA'd pioneer new drug, five to thirteen "me-too" copies were also brought on the market.[5]

Whether the manufacturers' individual exemption claims for "me-too" drugs were valid in most cases, and indeed whether FDA's overall treatment of "me-too" drugs was consistent with the statutory requirement of pre-marketing clearance for *all* "new drugs" were questions never considered or decided by any court. As a practical matter, FDA was forced by its limited resources and the overriding need to protect the public from dangerous new drug ingredients to adopt this short-cut approach to "me-too's", and the manufacturers had no cause to complain.

In 1962, Congress made three major changes in the 1938 Act it thought necessary to afford adequate protection to the public. Harris-Kefauver Amendments of 1962, 76 Stat. 781. First, the 1962 Amendments provided that no "new drug" could go on the market without *affirmative* approval by the FDA of the filed NDA. Second, they amended the definition of "new drug" to include any drug not already recognized by qualified experts as "safe *and effective*". Thus, as to drugs coming on the market for the first time after 1962, manufacturers would be required to file NDA's on all drugs not already recognized to be safe *and effective*; and for such drugs they would have to convince the FDA that such drugs were in fact both safe *and effective*. As we explain below, part III (A), the explicit efficacy requirement is not just a means of providing economic protection to consumers but is an

[5] Brief for the United States in *Bentex*, at 7-8 and n. 16.

integral part of a genuine guarantee to the public that all drugs on the market are really safe. Third, Congress required that the safety and efficacy of "new drugs" be demonstrated by "substantial evidence." In furtherance of this goal, it defined with great care in the Amendments what type of evidence would be considered in evaluating efficacy: only "adequate and well controlled [scientific] investigations" could be accepted by FDA in support of manufacturers' claims. FDA was also given power to promulgate regulations to implement these new provisions.[6]

With respect to drugs that were already on the market before 1962, Congress thought it would be unfair to apply the new efficacy standard to those that had never been subject to "new drug" pre-market clearance under the 1938 Act because they were already generally recognized as "safe" when first marketed (so long as manufacturers did not suddenly begin making new claims of effectiveness for these drugs). Consequently, Congress added to the Act § 107(c)(4), exempting from the 1962 amendments drugs that (A) were sold in the United States prior to 1962, (B) were not "new drugs" under the original Act, i.e., were generally recognized as safe *and* (C) were "not covered by an effective [new drug] application." As the Senate Committee Report put it:[7]

> Drugs which are used commercially at the time of enactment and which were never subject to the "new drug" procedure before, shall not be considered "new drugs" by reason of the new "effectiveness" requirements added . . . by the bill.

In explaining this clause on the Senate floor, Senator Eastland said: "Established drugs which have never been required to go through new drug procedures will not be

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[6] § 701(a), 21 U.S.C. § 371(a).

[7] S. Rep. No. 1744, part 2, 87th Cong., 2d Sess. at 5.

affected by the new effectiveness test insofar as their existing claims are concerned." 108 Cong. Rec. 17366.

But, as to drugs that were not generally recognized as safe when first marketed between 1938 and 1962 and had therefore come within the purview of the 1938 Act's pre-marketing clearance procedures, Congress determined that the new efficacy standard *should* apply. Manufacturers of such pre-1962 drugs already cleared for safety were given a two-year grace period to perform or commission whatever studies might be necessary to produce evidence of efficacy and submit such evidence to FDA. During the interim, they could remain on the market. Then, beginning in 1964, the Amendments mandated FDA in no uncertain terms to withdraw outstanding clearance to previously approved pre-1962 "new drugs" for which there was no "substantial evidence" of efficacy as carefully defined in the statute, and to take such drugs off the market.

Although Congress clearly intended that beginning in 1964 ineffective pre-1962 drugs would be removed from the market, the fact is that the 1962 Drug Amendments remain substantially unenforced as to such drugs ten years later. *American Public Health Association* v. *Veneman, supra.* FDA did little concerning pre-1962 drugs until 1966. It then referred the preliminary task of evaluating the efficacy of these drugs to a specially established Drug Efficacy Study Group of the National Academy of Sciences—National Research Council (NAS-NRC), to whose 30 expert panels manufacturers submitted their evidence concerning their drugs' effectiveness. The NAS-NRC Study Group considered approximately 4000 pre-1962 "new drugs" with were still being marketed and on which effective NDA's were still outstanding. (The Study Group did not specifically consider any "me-too" drugs that had not been NDA'd.) On account of its rigor and the prestigious credentials of its

panel members, the Study Group's evaluation has been generally regarded as one of the most thorough and unassailable of its kind ever conducted. Of the more than 16,000 claims of effectiveness made for the 4000 drugs the Group considered, it found that less than 30% were supported by "substantial evidence" as defined in the Act. See Brief for the United States in *Bentex*, at 18-19.

Not until 1968 and 1969 did FDA begin to take action with respect to these ineffective pre-1962 drugs. Of the 70% of claims found by the NAS-NRC to be unsupported by "substantial evidence," or up to 2800 ineffective NDA'd pre-1962 drugs, FDA has issued "opportunity for hearing" notices to only about 1300, and notices of withdrawal to only about 570.[8]

Nine months ago, in an action instituted by two of the *amici curiae*, the United States District Court for the District of Columbia held that the FDA had engaged in "intolerable procrastination" in evaluating the Study Group's reports, that hearings have been subject to "interminable delay", that FDA had extended the two-year grace period provided by Congress "far beyond that envisioned by statute," and that it had "effectively stay[ed] implementation of the Congressional mandate that drugs in the market-place be both safe and effective." *American Public Health Association* v. *Veneman*, CA No. 1847-70 (August 23, 1972). The Court retained jurisdiction and established a time schedule for FDA to complete its enforcement of the 1962 Amendments as to pre-1962 drugs. (Order of Bryant, J., October 11, 1972).

Thus, eleven years after Congress acted to remove ineffective drugs from the market, and nine years after the date Congress set for accomplishment of that task thousands—if "me-too's" are included, tens of thousands—

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[8] Information received March 27, 1973, by *amici* from FDA's Office of the General Counsel.

of ineffective pre-1962 drugs are still being sold throughout the country to unsuspecting consumers.

Enforcement of the 1962 Amendments against these pre-1962 ineffective drugs is no mere "residual" problem, for pre-1962 drugs constitute the vast bulk, perhaps 75-90%, of all prescription drugs on the market today.[9]

II. THESE CASES PRESENT THREE DISTINCT BUT INTERRELATED LEGAL ISSUES THAT ARE CRUCIAL TO MEANINGFUL ENFORCEMENT OF THE 1962 AMENDMENTS.

The four cases now before the Court raise three distinct legal issues concerning enforcement of the 1962 Amendments with respect to pre-1962 "new drugs". Simply stated, these are:

> (1) Whether pre-1962 "me-too" drugs (for which manufacturers never formally submitted NDA's, but which were marketed on the strength of the NDAs granted their "pioneers") can escape the efficacy requirement of the 1962 Amendments by virtue of § 107(c)(4).[10]

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[9] According to information received by *amici* from FDA's Office of the General Counsel, since 1962 FDA has received only 3450 NDA's and has approved only 578 of them. Since there are still well over 2000 pre-1962 NDA'd drugs on the market, and five to 13 times as many copies of these pre-1962 drugs, see p. 13, *supra*, it is not unreasonable to estimate that 75-90% of all prescription drugs now on the market are pre-1962 drugs.

The Act is also applicable to the 100,000 to 500,000 over-the-counter drugs sold in the United States today, a substantial percentage of which may be ineffective. Enforcement against over-the-counter drugs is discussed in part III(D) of this brief, *infra*.

[10] A subsidiary issue is raised by some manufacturers' claims that a good many "new drugs" on which NDA's were actually outstanding in 1962, when the Amendments went into effect, should also be immune from the new efficacy requirements. See notes 11 and 14, *infra*.

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[10] A subsidiary issue is raised by some manufacturers' claims that a good many "new drugs" on which NDA's were actually outstanding in 1962, when the Amendments went into effect, should also be immune from the new efficacy requirements. See notes 11 and 14, *infra*.

(2) Whether the FDA can perform the fundamental jurisdictional function of deciding, in the first instance, whether a drug is a "new drug" within the purview of the Act's pre-clearance provisions, or whether FDA has no power to determine its own jurisdiction.

(3) Whether FDA must afford a full-scale evidentiary hearing in every case before withdrawing approval of an NDA for an ineffective drug, even though the manufacturer has not submitted any evidence of effectiveness whatsoever that falls within the statutory and regulatory definitions of the type of evidence that can permissibly be considered in support of an efficacy claim.

The first issue, whether pre-1962 "me-too" drugs can escape the effect of the 1962 Amendments, arises principally in the *USV* case. Before 1962, USV marketed five citrus flavonoid drugs under outstanding NDA's and two similar "me-too" flavonoids for which it had never applied for NDA's. In 1968, FDA sought to withdraw approval of three of the five NDA's on the ground that citrus flavonoids are ineffective. It announced its view that, if successful, it would seek to remove the "me-too" flavonoids from the market as well. USV sought a declaratory judgment in District Court that all seven drugs were no longer "new drugs" in 1962 because all had become "generally recognized" as safe, and, under § 107(c)(14), were therefore not subject to the 1962 Amendments. The District Court agreed. But the Fourth Circuit reversed. It held (1) that the NDA'd drugs were clearly subject to the 1962 Amendments and (2) that although, ordinarily, "me-too" drugs never specifically covered by an NDA would not be subject to the new efficacy requirements, these particular "me-too's" were "personal" to the

company and were thus "covered" by the original NDAs on the same company's pioneer (NDA'd) drugs.[11]

The second issue, whether FDA has jurisdiction to determine what is a "new drug" under the Act, is posed in two distinct ways by the *Ciba* and *Bentex* cases, respectively: (a) whether FDA disapproval of a filed NDA operates as a judgment that the drug was in fact a "new drug" and that the NDA was in fact required to be filed under the Act, and (b) whether, when a manufacturer bypasses the FDA by failing to file an NDA and instead seeks a declaratory judgment in court that its drug is not a "new drug", the court can refer that question to the FDA for decision in the first instance.

Bentex marketed a "me-too" copy of a pioneer pentylenetetrazol combination drug on which three other companies held NDA's. In 1968, FDA sought to withdraw approval of the three NDA's, offering an opportunity for a hearing to any parties that would be "adversely affected" by such action. It issued an advisory inviting Bentex to participate in this hearing and stating its intention to withdraw Bentex's "me-too" from the market once the other manufacturers' NDA's were disapproved. Bentex and other "me-too" manufacturers then sought a District Court declaratory judgment that their "me-too's"

[11] The subsidiary issue, note 10, *supra*, is raised by USV's claim that not only its "me-too's" but at least two and possibly all five of its NDA'd drugs are also exempt. The rationale for this apparent evasion of the statutory language is that at some time before 1962 the NDA'd drugs, by virtue of their clearance and subsequent sale, became "generally recognized" as safe, were thus no longer "new drugs", and did not really need to be NDA'd any longer; consequently, the NDA's apparently covering them in 1962 were no longer "effective", and the 1962 Amendments do not apply. See note 14, *infra*.

Hynson, in its cross-petition, No. 72-414, makes a similar claim for its drug Lutrexin.

Bentex also involves a "me-too" drug, but only threshold jurisdictional questions are presented to this Court in that case.

were not "new drugs". The District Court held that both it and FDA had concurrent jurisdiction to decide this question and, in the exercise of its equitable powers, referred the issue to FDA for decision in the first instance. The Court of Appeals reversed and remanded, holding that the District Court had exclusive jurisdiction to decide the matter and should do so itself.

Ciba marketed its drug Ritonic under an effective NDA beginning in 1958. In 1969, the FDA sought to withdraw approval of the NDA for lack of substantial evidence of effectiveness. At this point, Ciba began a declaratory judgment suit in District Court for a declaration that Ritonic had, before 1962, ceased to be a "new drug". (Meanwhile, the FDA withdrew its approval, Ciba took a direct appeal from this withdrawal to the Second Circuit Court of Appeals, and that Court affirmed the FDA's action. *Ciba-Geigy Corporation* v. *Richardson*, 446 F.2d 466 (C.A. 2, 1971). FDA moved to dismiss the District Court action on the ground that, in the withdrawal proceedings, it had already determined the underlying issue adversely to Ciba. The District Court agreed and dismissed the action, and the Court of Appeals for the Third Circuit affirmed.[12]

The third or "hearing" issue arises in *Hynson*, No. 72-394. In May, 1970, the FDA promulgated regulations establishing minimum standards for "adequate and controlled investigations" required by the statute to be submitted in support of claims of "substantial evidence" of efficacy. 21 C.F.R. § 130.12(a)(15), as amended, 35 Fed. Reg. 7251, 7252. These regulations listed specific criteria for such evidence and provided, *inter alia*, that if a man-

[12] The second issue purportedly arises in *Hynson* as well, where the manufacturer is in the peculiar position of supporting FDA jurisdiction. But it is presented in a peripheral and beclouded fashion, and the courts below did not see fit even to address the question there.

ufacturer submitted no data meeting these criteria FDA would not hold an evidentiary hearing since there would in fact be nothing to hold a hearing about. Hynson, after losing (on primary jurisdiction grounds) a declaratory judgment action by which it sought District Court exemption for its drug Lutrexin (*Hynson*, J.A. I, 26), then sought a hearing from the FDA on "substantial evidence" of Lutrexin's effectiveness. After examining the evidence submitted by the company, however, FDA determined that each item failed to meet the criteria set out in the regulations; consequently, it denied Hynson a full evidentiary hearing. On petition for review, the Court of Appeals for the Fourth Circuit reversed. While ostensibly approving the FDA's regulations, the Appeals Court thought that Hynson's evidence presented a "genuine and substantial issue of fact" whether Lutrexin was "effective", and therefore Hynson should get a full evidentiary hearing.

III. A DECISION ADVERSE TO FDA ON ANY OF THESE ISSUES WILL, AS A PRACTICAL MATTER, PREVENT EFFECTIVE ENFORCEMENT OF THE ACT AND THWART THE CONGRESSIONAL PURPOSE TO REMOVE INEFFECTIVE DRUGS FROM THE MARKET.

Each of the three legal issues identified above is an essential part of a single unified approach adopted by FDA to carry out the intent of Congress manifested in the 1962 Amendments. Determination of any one of these issues adversely to FDA will, as a practical matter, operate to defeat the whole approach and prevent effective enforcement of the Act. As a result, most ineffective drugs now being sold to consumers will remain on the market indefinitely. Moreover, enforcement of the Act with respect to "new drugs" coming on the market for the first time now and in the future would also be threatened.

A. The Efficacy Requirement Added By The 1962 Amendments Is An Important Protection For Consumers.

The 1962 Congressional mandate that all drugs be not only "safe" but "effective" was not designed only to protect consumers' economic interests, though that is obviously one of its benefits. Congress and FDA recognized early on in their experience with the 1938 Act that a drug's effectiveness is often related to its safety, in the broadest medical and consumer sense.

A drug's effectiveness is an important consideration to be taken into account when it is known to have serious side effects. More generally, however, we are increasingly coming to realize that *all* drugs involve some risk of danger to some persons under some circumstances. The risk to all consumers is increased many-fold—and is not acceptable—when they are encouraged to consume a vast quantity of drugs that are really ineffective. Moreover, in many cases reliance on an ineffective drug excludes or makes less likely administration of an alternative drug (or therapy) that is badly needed and *would* be effective, thus posing a direct threat to health or, in the case of life-threatening diseases, to life itself.

B. A Decision Adverse To FDA Will Frustrate Enforcement Of The 1962 Amendments As To Pre-1962 Drugs.

(1) *If "Me-Too's" Are Exempt From The 1962 Amendments.*—As noted above,[13] the vast majority of prescription drugs now on the market were introduced prior to 1962 and most of these are "me-too" drugs not specifically being marketed under approved NDA's. If the 1962 Amendments are held applicable only to NDA'd pioneers, but not to the vastly larger number of copies

[13] See p. 17 and note 9, *supra*.

produced by other companies or under different names, as the Fourth Circuit has held, FDA will be unable to protect consumers from the thousands of ineffective pre-1962 drugs currently on the market, contrary to what Congress plainly intended. Moreover, manufacturers of ineffective NDA'd pioneer drugs will simply stop marketing them, rather than face up to the new statutory requirements, and will shift their production, advertising, and marketing to non NDA'd "me-too's" which need never be shown effective under such a ruling. The few manufacturers who had not marketed copies of their own pioneer drugs will, of course, lose out. But their competitors who do market the pioneer's copies (very often the identical drug under license from the manufacturer of the pioneer) will undoubtedly take up the slack. The public, therefore, will lose out in every instance—for the great majority of versions of every single ineffective "new drug" now being sold to consumers will remain on the market indefinitely.[14] No reasonable argument has been advanced, on health or other public policy grounds, why only a few of these ineffective drugs but not the majority of drugs that are identical or substantially similar to them should be removed from the market; or why Congress would intend such a result.

(2) *If the FDA Cannot Determine Its Own Jurisdiction.*—Even if the Court agrees with FDA that pre-1962 "me-too's" should be treated on an equal footing with their NDA'd pioneers, but holds that only courts—not FDA—can decide what drugs are covered by the

[14] *A fortiori*, if this Court accepts the claims of USV and Ciba that even their NDA'd drugs should be exempted, the 1962 Amendments will be rendered a practical nullity with respect to pre-1962 drugs. Almost every pre-1962 NDA'd drug that had been marketed for any substantial period of time arguably falls within that rubric. The "exception" provided by § 107(c)(4) would then swallow the whole by exempting almost all pre-1962 NDA'd drugs as well as all of their copies.

Amendments, FDA's enforcement effort against pre-1962 drugs could be long delayed or even rendered futile. And the courts will be flooded with litigation turning on highly technical medical, chemical, and pharmacological evidence.

Petitioner in *Ciba* argues that FDA disapproval (for lack of efficacy) of an NDA filed and approved by FDA prior to 1962 does not establish that the drug was really a "new drug" for which an NDA had to be filed in the first place, and that only a District Court is entitled to determine that jurisdictional point. If this Court holds that pre-1962 "me-too's" should be treated like their pioneers, but agrees with Ciba, then every manufacturer of a pre-1962 NDA'd drug whose clearance is now withdrawn by FDA (and who fails to win reversal of FDA action on petition for review to the Court of Appeals) will be entitled to litigate *de novo* in the District Court the question whether its drug was a "new drug" subject to the 1938 Act in the first place. Since this result would accord manufacturers a 'free second chance', several thousand District Court actions are likely. In each, the District Court will be obliged to consider a mass of pre-1962 medical and pharmacological data, and to determine whether at some point prior to 1962 the NDA'd drug became "generally recognized" by "qualified experts" as "safe". A judgment for the manufacturer in such a case would render the prior lengthy administrative proceeding concerning the drug's efficacy, and Court of Appeals review of that decision, a mere irrelevancy.

This Court could (and should) foreclose this possibility by holding, in accord with clear Congressional intent, not only that pioneers and copies should be treated alike but also that *all* pre-1962 drugs on which NDA's were outstanding in 1962 (and all their copies) automatically are subject to the efficacy requirements.

Such a holding might not, however, entirely counteract the effect of the Fourth Circuit's jurisdictional ruling in

Bentex. There, manufacturers of "me-too's" that had never been NDA'd sought a court judgment that their drugs were not "new drugs" and were not covered by the Amendments. The Fourth Circuit held that the threshold jurisdictional question could not be referred to the FDA but must be decided by the District Court. Presumably a decision by this Court that all copies of NDA'd pioneers are definitely covered by the Amendments would deprive "me-too" manufacturers of the core of their legal argument. But who is to decide when a drug is really a "me-too", i.e., when it is so "substantially similar" to a pioneer that FDA's withdrawal of the pioneer operates as a judgment about the alleged copy as well? The import of *Bentex* is that only the courts—not FDA—have the power to decide when a drug is really a "me-too" and therefore, like its pioneer, should be treated as a "new drug".

Should the Court leave this loophole open, it is likely that most manufacturers of pre-1962 "me-too's" whose NDA'd pioneers are removed from the market will come to the District Courts seeking to show that their products are not really copies but are in some way different from the pioneers, thus ought not to be characterized (like the pioneers) as "new drugs", and should not be subjected to the efficacy requirements. This could involve the District Courts in a deluge of tens of thousands of actions. Under the ruling in *Bentex*, the District Courts would apparently have no option to transfer the technical issue involved to FDA. They would have to decide it themselves, on the basis of medical, chemical, and pharmacological data of the type FDA regularly considers in making judgments about these drugs, but with which courts are simply not equipped to deal.

The only sensible approach to these problems is for District Courts to refer to FDA, for decision in the first instance, the questions of whether a drug is a "new

drug", and whether a purported copy is indeed "substantially similar" to its pioneer. These are precisely the types of judgments administrative agencies are supposed to make and can make, especially where scientific information of such a highly technical nature is involved, as here.

Retention of this jurisdictional power in FDA will preserve judicial review of the agency's judgments, both on petition for review to the Court of Appeals from disapproval of an NDA (available to both the pioneer and to all manufacturers of copies, who are invited under FDA regulations to participate fully as parties, *see* 37 Fed. Reg. 23185, adding § 130.40 to 21 C.F.R.) and in actions for seizure or injunction by FDA when a "me-too" manufacturer refuses to withdraw his product. But the standard of review will be no different from that which courts are accustomed to employ in overseeing expert administrative agency action.

(3) *If Hearings Must Be Accorded In Every Case, However Pointless*—Finally, if this Court agrees that FDA has statutory authority and jurisdiction to enforce the 1962 Amendments against both pioneer and "me-too" drugs, but rules that FDA must afford a full-scale evidentiary hearing to every manufacturer who submits a mass of 'scientific' evidence in support of its product's efficacy even though none of that evidence meets the threshold criteria of the statute and regulations, FDA may never be able to fulfill its statutory responsibility.

Of the 4000 NDA'd drugs reviewed by the NAS-NRC Study, the effectiveness of only 434 was found to be supported by "substantial evidence". Thus up to 3500 ineffective NDA'd drugs are subject to withdrawal under the 1962 Amendments. If the decision of the Fourth Circuit in *Hynson* is upheld, the prospect that most manufacturers of these ineffective drugs will seek and be able to obtain full-scale evidentiary hearings and that thou-

sands of these hearings will have to be held, is not unrealistic. The clear import of the Fourth Circuit's view is that *any* manufacturer who produces a large quantity of evidence of any kind that, to the layman's eyes, seems to support the efficacy of its product will be entitled to a full-dress hearing. And almost every manufacturer that desires to keep marketing an ineffective pre-1962 drug will, in fact, be able to produce enough testimonial, anecdotal, and other unscientific evidence to meet the standard articulated by the Fourth Circuit.

The legislative history and the language of the Act itself, which the Fourth Circuit appears to have disregarded, establish that this is manifestly not what Congress intended. Congress was well aware that masses of documentary evidence, uncontrolled scientific studies, and reports of experiments lacking systematic selection procedures and statistical analysis could be marshalled by most manufacturers, and sought statutorily to exclude such evidence from any consideration. Yet the Fourth Circuit's decision in *Hynson* reads out of the statute Congress's own definition of "substantial evidence" and replaces it with a judicially-fashioned, layman's definition that Congress deliberately rejected.

FDA simply does not have the resources or staff to hold in the next few years the thousands of pointless hearings that would be required if the Fourth Circuit's view is sustained. Some NDA's now run to 400 volumes of scientific data, and the average in 1970 was about 30 volumes, or a stack of paper 10-12 feet high. See Brief for the United States in *Bentex*, at 9, n. 18. The average time for a hearing may be as long as a month. FDA has noted that one recent hearing took three months to complete. *In the Matter of SERC Tablets, Unimed Inc.*, Docket No. FDCD-111, 1969.

Nor will FDA be able to comply with the implementation schedule imposed on it by the District Court in

American Public Health Association v. *Veneman, supra.* In its petition for a writ of certiorari in *Hynson*, the FDA stated that "[m]anifestly, the agency will be unable to satisfy the thrust of [the *Veneman* decision] to expedite review and appropriate withdrawal actions if it must meet the standard for granting evidentiary hearings prior to withdrawal that has been imposed [by the decision below]." In its brief as Petitioner in *Hynson*, the United States further observes that FDA is "currently laboring to carry out the court's order [in *Veneman*] punctually, but its efforts will be of little avail and of no benefit to the public if all that is accomplished is to bring nearer the holding of hundreds or thousands of pointless hearings." Page 30.

If this Court requires FDA to evaluate in full-scale evidentiary hearings evidence that Congress itself statutorily excluded in 1962 as inadequate, the Congressional intent will be subverted and the delay in enforcing the 1962 Amendments will be interminable.

C. An Adverse Decision Will Also Threaten Enforcement of the 1962 Amendments With Respect to Post-1962 Drugs.

The Fourth Circuit decisions also threaten to block effective enforcement of the 1962 Amendments with respect to "new drugs" now coming on the market.

FDA now regards all "me-too" copies of post-1962 "new drug" pioneers to be themselves "new drugs" requiring premarketing clearance.[15] Manufacturers of new "me-too's" must now file 'abbreviated' NDA's (which can refer to the pioneer) on each such drug. If, as USV and Ciba argue, *see* notes 10, 11, and 14, *supra*, marketing of a new drug pioneer for a short period of time under an effective NDA makes that drug *ipso facto* no longer

[15] 37 Fed. Reg. 23185, adding § 130.40 to 21 C.F.R.

a "new drug", and if copies introduced more than a few months or a year after the pioneer need not be NDA'd, then the reach of FDA's enforcement will extend to only a tiny fraction of the entire universe of "new drugs" coming on the market. And such a holding would simply encourage manufacturers to abandon pioneers after a short time and concentrate on marketing copies, which would not have to be subjected to pre-marketing clearance.

This result would undermine FDA's important "continuing enforcement" function. Section 505(e)(3) of the Act, as amended in 1962, now requires the Secretary to withdraw approval of an NDA if he finds on the basis of "new information" that the drug is not safe or effective. Continuing jurisdiction over NDA'd drugs is necessary to permit FDA to withdraw drugs hitherto thought to be safe and effective when new data comes to light casting doubt on this judgment (as it has in recent cases of food additives shown to be carcinogenic).

If FDA has no power to determine its own jurisdiction, the manufacturer of a "new drug" now being put on the market for the first time will be able to bypass or duplicate FDA clearance procedures and throw the resolution of the jurisdictional issue into the courts. For example, if the Court accepts the argument of petitioner in *Ciba*, drug manufacturers interested primarily in delay will routinely submit an NDA to FDA. Then, if FDA determines that substantial evidence of the drug's efficacy is lacking (and the Court of Appeals affirms), the manufacturer will simply repair to the District Court for a *de novo* determination of whether it had to file the NDA in the first place. The evidence considered by the District Court in deciding whether the drug was "generally recognized as safe and effective" will be virtually identical to that previously considered by FDA in determin-

ing the "substantial evidence" question.[16] If the Fourth Circuit's decision in *Bentex* is affirmed, manufacturers would have no obligation to go to FDA first but could seek a declaratory judgment in District Court that they were not required to file NDA's on particular products. The District Courts could not refer these disputes to FDA, under *Bentex*, but would have to do the FDA's job for it by deciding, on the basis of all the medical and scientific information, whether the drug was indeed a "new drug". Again, the evidence considered by the District Court would be roughly the same as the evidence the manufacturer would have submitted to FDA to show safety and efficacy had the manufacturer filed an NDA rather than gone to court.

Clearly Congress could not have intended such wasteful and confusing duplication or the ousting of FDA in favor of judicial determination of such complex technical and scientific questions.

D. The Fourth Circuit's Decisions, If Sustained, Will Undermine FDA's Aggressive New Effort to Enforce the Act, For the First Time, Against Over-The-Counter Drugs.

The 1938 Act and 1962 Amendments are fully applicable to over-the-counter (OTC) drugs, but as a practical matter FDA has never enforced the Act against these products. A substantial percentage of the 100,000 to 500,000 OTC drugs now on the market are probably ineffective, but FDA simply does not have the resources to deal with these drugs individually, as the Brief for the United States in *Bentex* points out (pp. 24-25).

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[16] *De novo* District Court consideration of whether the drug was a "new drug" would give the manufacturer a second chance at review of this precise question, since the jurisdictional issue can be raised in the Court of Appeals on petition to review FDA's disapproval of a filed NDA. See Brief for United States in *Bentex*, at 53-55.

In the past year, FDA has taken encouraging new steps to deal with ineffective OTC drugs. Pursuant to new regulations, 37 Fed. Reg. 85-86, 9464, 9475, FDA proposes to classify the various drugs by therapeutic class and to investigate the claims of each class to effectiveness. This is a sensible approach to OTC drugs because the dimensions of the "me-too" problem with respect to such drugs are so great. Hundreds or thousands of drugs marketed under different names by different companies in fact contain identical active ingredients, and many more are familiar combinations of active ingredients contained in many other products. FDA's investigations of OTC drugs will accomplish two important goals. First, they will identify potential subjects for misbranding actions and provide the scientific evidence of ineffectiveness FDA needs for such actions but seldom possesses.[17] Second, they will permit FDA in the future to classify as "new drugs" all OTC drug substances shown by the investigations to be ineffective and to prevent new versions or copies of these drugs from being marketed without express approval. The investigations, together with the new drug inventory required by the Drug Listing Act of 1972, 86 Stat. 559 (see Brief for the United States in *Bentex*, at 23-24), will also permit FDA to identify and withdraw from the market ineffective OTC drugs brought on the market after 1962 for which manufacturers never applied for NDA's.

The Fourth Circuit's approach to the Act would, however, blunt this significant new enforcement effort before it gets off the ground. If, as the Fourth Circuit believes, the Act permits FDA to deal only with an original pioneer and not with copies, and if FDA has no jurisdiction to decide what is a "new drug" or when a drug is a copy, then FDA's endeavor to classify and withdraw ineffec-

[17] See part III(e) of this Brief, *infra*.

tive OTC drugs will be jeopardized, if not doomed to failure.

As FDA recognizes, the "class" approach, which is perfectly consistent with the Act, is the only practical way to apply the Act to the vast number of outstanding and future OTC drugs.

E. Misbranding Actions Are No Substitute For The Efficacy Requirements Adopted In The 1962 Amendments.

Petitioner USV suggests (p. 64) that the FDA's statutory authority to deal with "misbranded" drugs, especially through an action for condemnation in District Court,[18] will be quite adequate to protect the public interest in drug efficacy if the 1962 Amendments are gutted by judicial action. Obviously, if Congress believed this to be the case it would never have enacted the 1962 Amendments, and if FDA thought "misbranding" actions were effective tools it would not be attempting to enforce the 1962 Amendments.

In fact, for two reasons, the misbranding action is so difficult and drawn out that it is practically useless. First, the burden of proof in such an action is on the Government, and the task of proving positively that a drug is *in*effective (even by a preponderance of the evidence) is a considerable one. Second, in a court action there are no limitations on the type of evidence the manufacturer can submit, however unscientific it may be. A mass of testimonial and anecdotal evidence from doctors of the type Congress believed should not be considered by FDA to show efficacy can be introduced in court in defense of a misbranding action. This evidence may appear to judge and jury to be a powerful rebuttal to the Government's case.

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[18] 21 U.S.C. §§ 331(a), 334(a).

Consequently, to prevail in a misbranding action, the FDA has found it necessary to conduct its *own* careful scientific study of the drug in question to establish ineffectiveness. Such studies are costly and often take several years. And even a very good study may fail to impress the judge or jury in light of the mass of contrary (unscientific) evidence submitted by the manufacturer.

IV. FDA'S ENFORCEMENT PROGRAM IS TOTALLY CONSISTENT WITH THE STATUTORY LANGUAGE AND HISTORY.

A. Congress Intended The 1962 Efficacy Requirement To Apply To Both Previously NDA'd Drugs And Their Copies.

The legislative history of § 107(c)(4), discussed at pp. 14-15, *supra*, and in the Brief for the United States in *Bentex*, at 10-14, shows that Congress meant to exempt from the efficacy requirement only "old drugs"—those generally recognized as safe when first marketed—that had never come within the ambit of the "new drug" provisions of the 1938 Act. There is no extrinsic evidence to show that Congress was aware of the "me-too" problem or of the possibility that its exemption clause might be held applicable not just to old drugs but to copies of "new drugs". The best interpretation of what Congress intended is that which is most sensible and harmonious with the statutory purposes. Here, the interpretation most harmonious with the purposes of the Act is that Congress did not intend by § 107(c)(4) to provide a loophole for copies of "new drugs", but that it simply meant to exempt old drug substances that were never affected by the original clearance scheme. The contrary interpretation would not only defeat the purpose of the 1962 Amendments; it makes little practical sense. It would create the incongruity of having two different statutory clearance standards for the identical drug substance, depending on the name under which the substance was marketed. Which

standard was applicable would depend not on any rational or public policy ground, but on the regulatory history of the drug as determined by the manufacturer. The resulting irrational discrimination rebuts the notion that this is what Congress intended.

The language of § 107(c)(4) exempts only pre-1962 drugs that were not "covered by" an effective NDA. USV's lengthy argument that the NDA's covering pioneers were "personal" to those drugs, however valid, misses the point. The issue is what Congress *intended* by the words "covered by" as used in the section, words that appear nowhere else in the Act. Though most "me-too's" were marketed without the formal filing of applications for clearance, they were obviously marketed on the strength of the clearances previously granted their identical (or substantially similar) pioneers. As pointed out above, the only sensible interpretation of Congressional intent consistent with the purposes of the Act is that "me-too's" were "covered by" the NDA's of their pioneers, and that copies are no more exempt from the efficacy requirement than their pioneers just because they are marketed under different trade names.

The manufacturers argue that until recently FDA has appeared to adopt their view concerning the reasons NDA's were not required to be filed on most "me-too's" and that the agency has now changed its mind. Though FDA has altered its explicit requirements for filing of NDA's on "me-too" drugs, it appears to *amici* that in practical terms the agency has been perfectly consistent in its overall enforcement approach. Before 1962, when clearance of a filed NDA occurred automatically absent FDA objection, the FDA informally cleared "me-too" copies once the pioneer was cleared. By the terms of the 1938 Act, FDA should at least have required manufacturers of the copies to file abbreviated NDA's as it does now. But its failure to do so was primarily an accom-

modation to the manufacturers and had no adverse consequences to the consumer. The consumer was protected by the fact that the pioneer was required to be NDA'd. The pioneer and the "me-too's" rose and fell together.

In 1962, FDA was required by its new statutory mandate affirmatively to investigate the efficacy of all pre-1962 "new drugs." FDA again wishes to insure that pioneers and "me-too's" rise and fall together in order to protect the consumer. But it can no longer protect the consumer if it ignores the statutory scheme and does not formally designate "me-too's" as "new drugs". Therefore, FDA now correctly insists that "me-too's" are "new drugs" within the meaning of the 1938 Act and 1962 Amendments.

In short, FDA previously engaged in an administrative practice inconsistent with the terms of the 1938 Act as an accommodation to manufacturers and at no cost to consumers. The consumer, whom the Act seeks to protect, should not now be penalized for FDA's erroneous view of what the statute required it to do with respect to "me-too's". And FDA itself should not be prevented from now adopting a correct interpretation of the Act in order to fulfill its purpose of protecting consumers.

The change from prior improper practice does not prejudice those who contest the change or defeat any *reliance interest* they may have developed. The drug manufacturers have not acted or been encouraged to act in reliance upon FDA's previous administrative interpretation. If anything, they benefited from it undeservedly. The only interest they now assert is the interest in continuing to market ineffective drugs ten years after Congress directed that such drugs be taken off the market. It would not defeat any valid interest of the drug manufacturers for this Court to uphold FDA's present strict adherence to the statutory scheme and to prevent sub-

stantial detriment to the public resulting from FDA's erroneous past administrative practice.

USV's most vehement arguments are directed against actions FDA has not yet taken. (1) USV claims the FDA has no specific statutory authority to "withdraw" or force off the market a drug that has never been NDA'd. To the contrary, FDA does have power under the statute to go to court to do just that. And traditionally it has advised manufacturers whether their drugs are "new drugs", and thus need to be NDA'd. The obvious consequences of such an advisory opinion, if ignored, are that FDA may seek District Court action against the manufacturer. Thus FDA anticipates doing in the future only what it has been doing all along in order to make the system work for both the public and manufacturers. (2) USV also attacks the hearing procedures FDA intends to put into practice for adjudicating the efficacy of both a pioneer and its copies in a single proceeding. But these regulations are not before this Court, and their legal sufficiency can be challenged elsewhere.

B. FDA Has Jurisdiction To Decide, In The First Instance, What Is A "New Drug" And When A Drug Is A Copy.

Two jurisdictional issues are posed by these cases: whether FDA action on a filed NDA operates as a judgment that the drug was in fact a "new drug" for which an application had to be filed; and whether, when a drug manufacturer seeks a declaratory judgment in District Court that its product is not a "new drug", the Court may refer that question to FDA for decision in the first instance.

With respect to the first issue, the only sensible answer is that FDA does determine its own jurisdiction in the context of its own administrative proceeding. This conclusion is supported by precedent. This Court has, in-

deed, recently held that where an agency's threshold jurisdiction turns on technical questions of fact arguably within the competence of the agency, it "should at least be requested to institute proceedings" [in the course of which the agency would determine the question of its jurisdiction]. *Ricci* v. *Chicago Mercantile Exchange*, No. 71-858 (Jan. 9, 1973); *see Marine Engineers Beneficial Assn.* v. *Interlake S.S. Co.*, 370 U.S. 173; *Federal Power Commission* v. *Louisiana Power & Light Co.*, 406 U.S. 621 (1972). The conclusion is supported by logic, since the function of the administrative agency to resolve technical, factual issues requiring special expertise is equally applicable to determining, within a fairly broad scope, the facts upon which its jurisdiction depends. And the conclusion is supported by the nature of the decisions called for by the clearance scheme involved here. Under the 1962 Amendments, the "new drug" threshold jurisdictional issue (i.e., whether a drug is "generally recognized" as effective) and the "substantial evidence of effectiveness" issue are similar questions whose resolution turns upon practically the same evidence. Moreover, both turn on highly technical medical, chemical and pharmacological judgments. It would be unreasonable to assume that the Act obligates FDA to make one of these judgments but bars FDA from making the other judgment, permitting only a court to do that. We have argued in part III, *supra*, that this would be wasteful, confusing, and deleterious to enforcement of the Act. It would also be contrary to the well-established role of administrative agencies.

With respect to the second issue, District Court deferral to FDA is supported by all the considerations mentioned above. See also *Ricci* v. *Chicago Mercantile Exchange*, *supra*; *United States* v. *Western Pacific R. Co.*, 352 U.S. 59; *Far East Conference* v. *United States*, 342 U.S. 570. Moreover, referral is consistent with the overall

scheme of the Act. It encourages the manufacturer to go first to FDA with a new drug application, since the manufacturer knows that the agency will be deciding the issue in the first instance anyway. A contrary holding would tend to undermine the self-policing nature of the Act by permitting manufacturers to choose the forum they preferred for resolution of the "new drug" issue.

C. FDA Need Not Accord A Full Evidentiary Hearing When The Manufacturer Produces No Scientific Studies That Meet The Statutory And Regulatory Criteria.

Congress defined "substantial evidence" in the 1962 Amendments with a high degree of particularity, as the statutory language and legislative history (set out in the Government's Brief in *Hynson*, No. 72-394, at 15-17) demonstrate. Only "adequate and well-controlled investigations" could be accepted in support of efficacy claims. The Committee Report on the bill provides further details of what Congress meant by this definition:

> A claim could be rejected if it were found (a) that the investigations were not "adequate"; (b) that they were not "well-controlled"; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which the application is made; or (d) that the conclusions drawn by such experts could not fairly and responsibly be derived from their investigations. S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess., p. 6.

Congress was well aware that masses of documentary evidence, uncontrolled scientific studies, and reports of experiments lacking systematic selection procedures and statistical analysis could be marshalled by most manufacturers, and sought statutorily to exclude such evidence from any consideration. The Act authorizes FDA to promulgate regulations to implement the efficacy requirements, 21 U.S.C. § 371(a), and FDA's regulations set-

ting out criteria for "substantial evidence" are firmly rooted in the Act, the legislative history, and the best current scientific thinking. *See*, 21 C.F.R. 130.12(a)(15) and 130.14, as amended, 35 Fed. Reg. 7251, 7252. These regulations have uniformly been upheld by the courts [19] and are ostensibly not challenged here by any party.

However, the decision of the Fourth Circuit in *Hynson*, if allowed to stand, will nullify the regulations by reading out of the 1962 Amendments Congress's own definition of "substantial evidence" and replacing it with a generalized layman's definition that Congress deliberately rejected. The Fourth Circuit ruled that Hynson was entitled to a full evidentiary hearing because its evidence raised a "genuine issue of fact" concerning its drug's efficacy, even though FDA found none of this evidence to be of the type that was entitled to any consideration under the statute and regulations. By so holding the court addressed itself to the wrong question. The statute does not envisage that *any* number of inadequate, uncontrolled studies could be sufficient to show efficacy. The proper issue on review had nothing to do with what the studies showed (i.e., whether the studies presented some evidence of efficacy). The proper issue was whether they were the kinds of studies the statute and regulations permit FDA to consider in support of an efficacy claim. This is a *legal* question FDA must decide in the first instance. FDA's legal judgment is fully reviewable on appeal. But its determination that none of the studies presented by Hynson met the criteria for consideration compelled the conclusion that there was nothing before it upon which a determination of "substantial evidence" —as defined in the statute—could be premised. In similar contexts, the courts have upheld agency denial of a

[19] *Upjohn* v. *Finch*, 422 F.2d 944 (CA 6, 1970); *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del. 1970); *see also* cases cited in note 1, *supra*, and the decisions below in the instant cases.

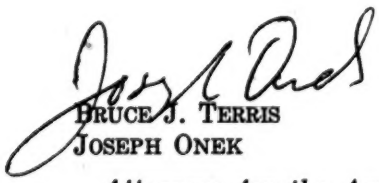
hearing. *See, e.g., Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33, and other cases cited in the Brief for the United States in *Hynson*, No. 72-394, at 22-23.

Consequently, FDA was perfectly correct in denying Hynson an evidentiary hearing in this case.

CONCLUSION

For the foregoing reasons, the judgments of the Courts of Appeals in *Hynson*, No. 72-394, and *Bentex*, No. 72-555 should be reversed, and the judgments in *USV*, No. 72-666, *Hynson*, No. 72-414, and *Ciba*, No. 72-528 should be affirmed.

Respectfully submitted,



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Letter from C. Joseph Stetler, President, Pharmaceutical Manufacturers Association, to Charles C. Edwards, M.D., Commissioner of Food and Drugs, dated June 3, 1970, attached as Exhibit 5 to the Complaint in *Pharmaceutical Mfrs. Ass'n* v. *Richardson*, Civ. No. 3946 (D. Del., filed July 22, 1970) 17

Letter from Charles C. Edwards, M.D., Commissioner of Food and Drugs, to C. Joseph Stetler, President, Pharmaceutical Manufacturers Association, dated July 8, 1970, attached as Exhibit 6 to the Complaint in *Pharmaceutical Mfrs. Ass'n* v. *Richardson*, Civ. No. 3946 (D. Del., filed July 22, 1970) 17, 18

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

Nos. 72-394, 72-414, 72-528, 72-555, 72-666

CASPER W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS,

Petitioners,

v.

HYNSON, WESTCOTT & DUNNING, INC.,

Respondent.

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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AND CONSOLIDATED CASES

MOTION FOR LEAVE TO FILE BRIEF FOR PHARMACEUTICAL MANUFACTURERS ASSOCIATION AS AMICUS CURIAE

Pursuant to Rule 42 of the Rules of this Court, the Pharmaceutical Manufacturers Association (PMA) hereby moves this Court for leave to file a single brief as *amicus curiae* in the above-captioned consolidated cases. The Solicitor General and counsel for Ciba Corporation, Bentex Pharmaceuticals, Inc. and USV Pharmaceutical Corporation have all consented to the filing of the attached brief at the time respondents' briefs are due.

Copies of the letters of these counsel consenting to the filing of this brief have been filed with the Clerk of the Court. The consent of counsel for Hynson, Westcott & Dunning, Inc., respondent in No. 72-394 and petitioner in No. 72-414, was requested but refused on the ground that PMA intended to take a position inconsistent with that of Hynson, Westcott & Dunning in No. 72-414. Hynson, Westcott & Dunning will in no way be prejudiced by the filing of PMA's brief at this time, however, since it will have an opportunity to file a reply brief in No. 72-414.

The interest of PMA as *amicus curiae* is set forth at pages 1-2 of the attached brief.

Respectfully submitted,

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April 2, 1973

IN THE

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OCTOBER TERM, 1972

Nos. 72-394, 72-414, 72-528, 72-555, 72-666

CASPER W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS,

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AND CONSOLIDATED CASES

BRIEF FOR PHARMACEUTICAL MANUFACTURERS ASSOCIATION AS AMICUS CURIAE

INTEREST OF AMICUS CURIAE

The Pharmaceutical Manufacturers Association (PMA) is a voluntary, nonprofit membership association com-

posed of more than 100 companies which account for approximately 95% of the production of prescription and ethically promoted over-the-counter drugs in the United States. PMA has often represented the interests of its member companies in both administrative and judicial proceedings.[1]

The cases now before this Court raise important issues about the correct construction and application of the provisions of the Federal Food, Drug, and Cosmetic Act dealing with "new drugs." PMA's member companies have a direct and vital interest in the resolution of those issues. PMA believes that it can assist the Court by presenting in a single *amicus* brief the views of the nation's manuufacturers of prescription and ethically promoted over-the-counter drugs on the complex and important issues at stake in these cases.

INTRODUCTION AND SUMMARY OF ARGUMENT

The issues presented by the cases now before this Court concern the provisions of the Federal Food, Drug, and Cosmetic Act dealing with "new drugs." Under the statute, it is illegal to market a "new drug" without approval of a new drug application (NDA) by the Food and Drug Administration (FDA). Sections 301(d), 505(a), 21 U.S.C. §§ 331(d), 355(a). From 1938 until 1962, this required a showing that the drug was safe for its recommended uses. Section 505, 52 Stat. 1052 (1938). Since 1962, the Act has required an additional showing of efficacy, based on a statutorily defined standard of "substantial evidence of effectiveness." Sections 505(d) and (e), 21 U.S.C. §§ 355(d) and (e).

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[1] See, *e.g.*, *Abbott Laboratories* v. *Gardner*, 387 U.S. 136, 156-57 n.20 (1967); *Pharmaceutical Mfrs. Ass'n* v. *Gardner*, 381 F.2d 271 (D.C. Cir. 1967); *Pharmaceutical Mfrs. Ass'n* v. *Richardson*, 318 F. Supp. 301 (D. Del. 1970).

However, under the statute not all drugs are "new drugs." From 1938 until 1962 a "new drug" was defined as one that was "not generally recognized as safe" by qualified experts. Section 201(p), 52 Stat. 1041 (1938). Since 1962, a "new drug" has been defined as one "not generally recognized as safe and effective" by qualified experts. Section 201(p), 21 U.S.C. § 321(p). Moreover, when Congress in 1962 amended both the "new drug" definition and Section 505 of the Act to include a new efficacy requirement, it enacted a "grandfather" provision permanently exempting certain products then on the market from the amendments to the "new drug" definition. 76 Stat. 788-89, note following 21 U.S.C. § 321.

Thus, the basic scheme created by the statute carefully distinguishes between "new drugs" and drugs that are not "new"—the latter being often referred to as "old" drugs. The cases now before this Court reflect the efforts of the FDA to transfer from the courts to the agency authority to determine whether a product is a "new drug," to sweep virtually all products into the "new drug" category, and to dispense with hearing rights in connection with proceedings to withdraw approval of new drug applications. As we will show in this brief, these efforts by the FDA are flatly inconsistent with the statute and are unnecessary to assure its effective implementation.

I.

The question of the FDA's authority to withdraw approval of a new drug application for lack of substantial evidence of effectiveness without providing a hearing on disputed, material issues of fact is presented in *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, No. 72-397. Section 505(e) of the statute, governing proceedings to withdraw approval of NDA's, provides the affected manufacturer a right to a hearing. A hearing, there-

fore, must be held whenever there is a genuine dispute as to material facts—*i.e.*, in this context, whenever a manufacturer sufficiently alleges facts which, if true, would support a finding of substantial evidence of effectiveness for the product in question. Where such a factual dispute exists, the Commissioner of Food and Drugs may not resolve that dispute before the hearing and invoke his resolution of the issue as his reason for denying a hearing. Moreover, under well-established principles of summary judgment procedure, the burden of establishing the lack of a material factual dispute is clearly on the Commissioner, as the party moving for summary judgment.

The FDA's hearing regulations purport to embody judicial summary judgment principles, and have been upheld by the courts only on that basis. The Fourth Circuit correctly set forth and applied those principles in its *Hynson, Westcott & Dunning* decision. In arguing that that decision was incorrect, the Government has blurred the distinction between the test for determining the issue of substantial evidence of effectiveness on the merits at a hearing and the test for determining whether the Commissioner is entitled to award himself summary judgment on that issue without a hearing. In so arguing, the Government has demonstrated that, despite the language of its regulations, the FDA's continued intention is to decide disputed questions as to the existence of substantial evidence of effectiveness in advance of a hearing and, on the basis of such findings, to determine that no hearing is necessary. Under such a regime, the right to a hearing guaranteed by the statute would be effectively, and illegally, obliterated.

II.

On the second major issue presented by these cases—whether the FDA has authority to make binding determinations whether a product is a "new drug"—there

is a conflict between the circuits. In *Ciba Corporation* v. *Weinberger*, No. 72-528, the Third Circuit affirmed the district court's refusal to issue a declaratory judgment on the "new drug" status of a product on the ground that the issue had been decided by the FDA, *sub silentio*, in a proceeding to withdraw approval of the NDA for the product. In *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72-555, the Fourth Circuit reached the opposite result, holding that it was improper for a district court to defer to the FDA's judgment on the "new drug" question, since the FDA had no authority under the statute to make such determinations. The Fourth Circuit followed its *Bentex* decision on the same issue in *Hynson, Westcott & Dunning, Inc.* v. *Weinberger*, No. 72-414, and in *USV Pharmaceutical Corp.* v. *Weinberger*, No. 72-666.

This conflict between the circuits should be resolved in favor of the carefully reasoned opinion of the Fourth Circuit in *Bentex*. The Food, Drug, and Cosmetic Act itself defines the term "new drug" (Section 201(p)), and makes it a prohibited act to market a "new drug" without a new drug application approved by the FDA. Sections 301(d), 505(a). But nowhere in the statute is the FDA given any authority to determine whether a product is a "new drug"; its only authority under the new drug provisions (Section 505) of the statute is to approve or disapprove a new drug application.

This does not make for an irrational or ineffective legislative scheme. A manufacturer who markets a product without an approved NDA in the face of the FDA's opinion that the product is "new" does so at his own risk—the very serious risk under Title III of the Act of seizure of the product or an action seeking an injunction against its marketing or even criminal penalties. This is consistent with the general scheme of the statute—reflected in the basic adulteration and misbranding provisions—under which standards of conduct are set forth

in the statute itself, with violations of those standards determined in judicial enforcement actions brought by the Government at the behest of the FDA.

Moreover, there is no basis for any suggestion that resolution of the "new drug" issue by the courts in declaratory judgment and enforcement actions is either novel or unduly difficult and burdensome. The fact is that the courts have been resolving these issues for many years without any perceptible difficulty or burden. In arguing that the question whether a product is a "new drug" is unduly complex and technical for a court, the Government ignores the critical distinction between that question and the question resolved by the FDA in determining whether or not to grant or continue approval of a new drug application. The test for approval of an NDA is actual safety and effectiveness, and requires a careful analysis of all relevant scientific evidence, including clinical tests. The question whether the product is a "new drug," by contrast, turns on whether the product is *generally recognized* as safe and effective. The latter issue has lent itself well to judicial determination.

The Government's bootstrap efforts to imply FDA authority to resolve the "new drug" issue in the course of passing on NDAs or, in other contexts, by issuing declaratory orders, founder on the simple and inescapable fact that the statutory scheme created by Congress deliberately allocates to the courts the decision whether a product is a "new drug." In the last analysis, the Government is seeking no less than an amendment of the basic structure of the statute—a result that it should not be permitted to achieve by litigation.

III.

When Congress enacted the 1962 Drug Amendments to require that "new drugs" be shown to be effective as well as safe, it also enacted a "grandfather" clause per-

manently exempting from the new effectiveness requirement certain products already on the market, so long as they continued to be recommended for the same uses. Section 107(c)(4) of the 1962 Amendments permanently exempts any such product that "on the day immediately preceding the enactment date (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act." 76 Stat. 789, note following 21 U.S.C. § 321.

In *USV Pharmaceutical Corp.* v. *Weinberger*, No. 72-666, the Fourth Circuit held that any drug that had *ever* been the subject of an NDA did not qualify for grandfather protection under Section 107(c)(4), even if it had become generally recognized as safe by 1962—unless the FDA had formally withdrawn approval of the NDA. At the same time, the Fourth Circuit held that so-called "me-too" products of other manufacturers, substantially identical in composition to the NDA'd "pioneer" product but never the subject of NDAs themselves, could qualify for grandfather protection. In this Court, the Government supports the Fourth Circuit's position on once-NDA'd products but argues that all me-too products should also be deemed to be "covered" by the NDA for the product to which they are similar.

Both the Fourth Circuit and the Government have construed Section 107(c)(4) arbitrarily and illogically. Properly construed, Section 107(c)(4) grandfathers any product that on the day before the effective date of the 1962 Amendments was generally recognized as safe and therefore no longer a "new drug." There is no meaningful sense in which a product no longer "new" can be said to be "covered by an effective NDA."

This construction of the grandfather clause gives effect to the fundamental legislative purpose underlying

the enactment of the new effectiveness requirements in 1962—that entirely new products and new claims for old products were to be subjected to the new effectiveness requirement, but that existing claims for old products were to be exempted. The construction urged by the Government, by contrast, would render Section 107(c)(4) entirely meaningless. Every drug first marketed between 1938 (when the "new drug" provisions were first enacted) and 1962 must at some time have been a "new drug" which could not lawfully have been marketed without an effective NDA. And under the Government's view, an NDA once effective is always effective and covers all me-too drugs. Accordingly, if the Government's position were adopted, no drug first marketed between 1938 and 1962 could meet the test of Section 107(c)(4), and that section would have no function whatever.

In its *USV* decision the Fourth Circuit recognized the plausibility of the argument advanced here that a drug that is no longer "new" should not be considered to be "covered" by an effective NDA. It rejected the argument solely on the ground that it would make surplusage out of the requirement of clause (C) of Section 107(c)(4) that the product not have been covered in 1962 by an effective NDA. This ground for decision cannot stand. For on analysis it becomes clear that clause (C) is equally surplusage both under the interpretation of the grandfather clause adopted by the Fourth Circuit and under the interpretation proposed by the Government. Since Section 107(c)(3) of the 1962 Drug Amendments makes clear that all drugs covered by an effective NDA are not permanently grandfathered (but were subjected to the new effectiveness requirement after a two-year grace period), Section 107(c)(4), *even without clause (C)*, could apply only to old drugs not covered by an effective NDA.

In short, the "surplusage" objection is equally applicable to the positions of the Government and the Fourth Circuit as it is to the argument contended for here. In-

deed, since Section 107(c)(3) governs all drugs that are covered by effective NDAs, there is no construction of Section 107(c)(4) under which clause (C) is not surplusage. Under the circumstances, this Court should adopt the interpretation of Section 107(c)(4) that gives it a meaningful function, that accords with the fundamental legislative purpose, and that avoids distinctions between NDA'd and me-too products. It should therefore hold that any drug that was generally recognized as safe on the day before the enactment of the 1962 Amendments cannot be considered to have been covered by an effective NDA on that date and is therefore grandfathered as to pre-1962 claims by Section 107(c)(4).

ARGUMENT

I. A Manufacturer is Entitled to a Hearing on any Genuine Issue of Material Fact Before Withdrawal of Approval of a New Drug Application.

Weinberger v. *Hynson, Westcott & Dunning, Inc.*, No. 72-394, raises the question whether the Commissioner may withdraw approval of a new drug application (NDA) for lack of substantial evidence of effectiveness, thus halting further marketing of a drug, without giving the manufacturer a hearing on disputed, material factual issues. The Fourth Circuit held that the Commissioner may not apply his "summary judgment" regulations[2] so as to deny a hearing where a manufacturer alleges and offers appropriate proof of facts which, if true, would support a finding of substantial evidence of effectiveness. *Hynson, Westcott & Dunning, Inc.* v. *Richardson*, 461 F.2d 215 (4th Cir. 1972) (J.A. 173).[3] That holding is clearly correct.

This Court has recognized as a fundamental aspect of due process of law that a person has a right to a

[2] 21 C.F.R. § 130.14.

[3] "J.A." refers to the Joint Appendix filed in these consolidated cases.

hearing in advance of a decision by an administrative agency resolving disputed factual questions affecting his substantial rights. Due process entitles him to an opportunity to present his case on disputed issues, to confront the Government's case, and to cross-examine its witnesses. "In almost every setting where important decisions turn on questions of fact, due process requires an opportunity to confront and cross-examine adverse witnesses." *Goldberg* v. *Kelly*, 397 U.S. 254, 269 (1970). This is true not only where personal rights are at stake[4] but also where property rights are involved.[5]

The Food, Drug, and Cosmetic Act recognizes this constitutional principle by providing a hearing in a number of contexts to persons whose rights would be substantially affected by Government actions under the Act. *E.g.*, §§ 505(e), 507(f), 701(e), 21 U.S.C. §§ 355(e), 357(f), 371(e). Section 505(e) of the Act, which is involved in this case, guarantees "due notice and opportunity for hearing to the applicant" before the FDA may withdraw approval of an NDA. It reflects Congress' judgment that an opportunity for a hearing is appropriate before the FDA takes the drastic action of halting the manufacturer's further sale and the public's continued use of a drug already on the market.[6]

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[4] See, *e.g.*, *Bell* v. *Burson*, 402 U.S. 535, 539-42 (1971); *Boddie* v. *Connecticut*, 401 U.S. 371, 374-79 (1971).

[5] See, *e.g.*, *Greene* v. *McElroy*, 360 U.S. 474, 496-99 (1959) and cases cited at p. 497; *Morgan* v. *United States*, 304 U.S. 1, 14-15, 19 (1938); *ICC* v. *Louisville & Nashville R. Co.*, 227 U.S. 88, 93-94 (1913); *Hornsby* v. *Allen*, 326 F.2d 605, 608 (5th Cir. 1964); *Philadelphia Co.* v. *SEC*, 175 F.2d 808, 817 (D.C. Cir. 1948), *vacated as moot*, 337 U.S. 901 (1949). See generally K. DAVIS, ADMINISTRATIVE LAW §§ 7.01, 7.04 (Supp. 1970). Indeed, this Court based its holding in *Goldberg* v. *Kelly*, *supra*, on earlier business cases.

[6] The legislative history of the 1962 Amendments makes plain that Congress regarded an "opportunity for hearing" as required by basic fairness before the drastic action of removal of a drug from the market. Section 507(f), which authorizes removal of anti-

A summary judgment procedure does not carve out an exception to this right to a hearing. It merely recognizes that an evidentiary hearing is unnecessary where the material facts are not in dispute. See, *e.g.*, K. DAVIS, ADMINISTRATIVE LAW §§ 7.01, 7.04 (Supp. 1970); 6 J. MOORE, FEDERAL PRACTICE ¶ 56.06 (2d ed. 1972). The leading decision on hearing rights under the Food, Drug, and Cosmetic Act recognizes that the permissibility of denying a hearing hinges on the absence of any disputed issues of material fact. *Dyestuffs & Chemicals, Inc.* v. *Flemming*, 271 F.2d 281 (8th Cir. 1959), *cert. denied*, 362 U.S. 911 (1960). The court held that the FDA might deny a hearing (under Section 701(e) of the Act) where a manufacturer's allegations, even if true, would be legally insufficient to justify the relief sought. In other words, the factual issues raised by the objections had to be *material* issues—ones that went to the legality of the FDA's proposed action.[7]

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biotics from the market for lack of substantial evidence of effectiveness, does not, like Section 505(e), provide for a hearing in unqualified terms but provides for a hearing if the manufacturer states "reasonable grounds" for one. 21 U.S.C. § 357(f). Yet, in explaining Section 507(f), Senator Kefauver, chief sponsor of the 1962 Amendments, stated:

> "There of course would be public procedure with an opportunity for hearings and judicial review afforded the drug manufacturers before the FDA began this type of action." 108 CONG. REC. 22039 (1962).

[7] In the *Dyestuffs* case, it had already been established by a Supreme Court decision (*Flemming* v. *Florida Citrus Exchange*, 358 U.S. 153 (1958)) that, as a matter of law, color additives that were toxic at any level of concentration were not "harmless" and were legally barred from certification. The manufacturer's objections to the decertification order in *Dyestuffs* advanced several reasons for permitting the use of the additives in question, but did not allege that the additives met the legal test of harmlessness. Since it was clear that the manufacturer's objections were legally irrelevant, the court ruled that the FDA was justified in not holding a hearing that could not affect the FDA's final decision. See also *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192, 205 (1956); *FPC* v. *Texaco, Inc.*, 377 U.S. 33, 39 (1964).

The *Dyestuffs* decision reflects the basic principle embodied in the familiar summary judgment procedure of Rule 56 of the Federal Rules of Civil Procedure and the cases applying that rule: A party's right to a hearing turns on the existence of a disputed issue of fact bearing on his right to relief under applicable law. "The question presented by a motion for summary judgment is whether or not there is a genuine issue of fact, and not how that issue should be determined." 6 J. MOORE, *supra*, ¶ 56.11[3], at 2174, quoting *Koepke* v. *Fontecchio*, 177 F.2d 125, 127 (9th Cir. 1949). See also *Toebelman* v. *Missouri-Kansas Pipe Line Co.*, 130 F.2d 1016, 1018 (3rd Cir. 1942).

The FDA may not, in deciding on the need for a hearing under Section 505(e), resolve genuine factual disputes concerning the existence of substantial evidence of effectiveness:

> "Summary judgment procedures . . . do not replace the trial. Genuine and disputed questions are not to be decided on the paper record of affidavits and depositions . . . ." *Clayton* v. *James B. Clow & Sons*, 154 F. Supp. 108, 112 (N.D. Ill. 1957).

Professor Moore has stressed this point in summarizing the law under Rule 56:

> "The court is authorized to examine proffered materials extraneous to the pleadings, not for the purpose of trying an issue, but to determine whether there is a genuine issue of material fact to be tried." 6 J. MOORE, *supra*, ¶ 56.04, at 2060. See also *id.*, ¶ 56.11 [1.-2], at 2145; *id.*, ¶ 56.15, at 2281.

Nor may the FDA place the burden of establishing that there *are* genuine factual disputes on the manufacturer. Under well-settled principles, the Commissioner has the burden of establishing that there is no factual issue requiring a hearing, and all doubts about the

existence of a factual issue must be resolved against him. This is true regardless of who has the final burden of proof on the issue of substantial evidence of effectiveness of the drug.* "[T]he burden to show that there is no genuine issue of material fact rests on the party moving for summary judgment, whether he or his opponent would at trial have the burden of proof on the issue concerned; and rests on him whether he is by it required to show the existence or non-existence of facts." 6 J. MOORE, *supra*, ¶ 56.15[3], at 2342-43 (footnotes omitted). See also *id.* at 2335. This Court has stressed that, since the burden rests on the moving party, the materials on which he relies "must be viewed in the light most favorable to the opposing party." *Adickes* v. *S. H. Kress & Co.*, 398 U.S. 144, 157, 158-59 (1970); *United States* v. *Diebold, Inc.*, 369 U.S. 654, 655 (1962). "All doubts as to the existence of a genuine issue as to a material fact must be resolved against the party moving for a summary judgment." *Cameron* v. *Vancouver Plywood Corp.*, 266 F.2d 535, 540 (9th Cir. 1959); see 6 J. MOORE, *supra*, ¶ 56.06[2], at 2080; ¶ 56.11[3], at 2170 & n.27; ¶ 56.15[3].

This rule is particularly important where, as here, the critical decision whether there is a genuine issue of material fact requiring a trial is not made by a neutral trier of fact (such as an independent hearing examiner or administrative judge) but by one of the antagonists—the Commissioner, who is the very party seeking sum-

* The lower federal courts have concluded that the applicant has the burden of establishing the efficacy and safety of his drug when he seeks initial approval of an NDA. See *Ubiotica Corp.* v. *FDA*, 427 F.2d 376, 378 (6th Cir. 1970). However, contrary to the Government's assertion (Brief for Petitioners in No. 72-394, at 27), the burden shifts once a drug has begun to be marketed under an approved NDA. Where the FDA seeks to withdraw a previously granted approval, it has the burden of showing that the drug does not meet the statutory tests. *Bell* v. *Goddard*, 366 F.2d 177, 181 (7th Cir. 1966).

mary judgment. The Commissioner, under his procedural rules, is allowed to award summary judgment to himself. Under these circumstances, courts have a special duty to review most carefully how the Commissioner, acting as both movant and judge, decides his own motion in his own favor.[9]

The courts have confirmed that this elementary burden-of-proof rule applies when summary judgment is sought in an administrative proceeding as well as in a court action. See, *e.g.*, *NLRB* v. *Smith Industries, Inc.*, 403 F.2d 889, 892-95 (5th Cir. 1968). Indeed, the Court of Appeals for the District of Columbia Circuit has applied the rule to proceedings for withdrawal of NDA approvals. In *USV Pharmaceutical Corp.* v. *Secretary of Health, Education & Welfare*, 466 F.2d 455, 461 (D.C. Cir. 1972), it held that the rule is "basic to ad-

[9] Indeed, a strong argument could be made that, in adapting the summary judgment procedure to the context of an administrative proceeding, the FDA ought to have a neutral hearing examiner initially decide whether there is a genuine issue of material fact. Under the FDA's regulations, hearings on withdrawals of approval of NDAs are conducted not by the Commissioner but by an independent hearing examiner appointed pursuant to Section 5(d) of the Administrative Procedure Act, 5 U.S.C. § 554(d). 21 C.F.R. § 130.17. Fairness would dictate that the function of deciding whether a triable issue of fact exists should also be assigned initially to the hearing examiner.

The Administrative Conference of the United States has recommended that agencies adopt a summary judgment procedure under which the decision to grant summary judgment would be made by the "presiding officer," not by the moving party. Administrative Conference of the United States, Recommendation No. 20 (adopted June 1970). A commentary prepared by the draftsmen of the recommendation does not even consider entrusting the authority to grant summary judgment to anyone but the hearing officer. Gellhorn & Robinson, *Summary Judgment in Administrative Adjudication*, 84 HARV. L. REV. 612 (1970). If the FDA's procedure followed the Administrative Conference recommendation, it would avoid the evident unfairness of permitting the Commissioner, as an interested party, to pass in the first instance on his own motion for summary judgment.

ministrative fairness" and is fully applicable to withdrawal proceedings under Section 505(e). In that case, the court invalidated the FDA's withdrawal of approval of three NDAs because, *inter alia*, the Commissioner had failed to meet his "obligation to present at least a prima facie case for denial of a hearing." *Id.* The Government, which did not seek review of that decision by this Court,[10] now takes issue with this aspect of the decision, or at least suggests that the Commissioner should have been permitted to rely on the NAS-NRC reports to make out his *prima facie* case. Brief for Petitioners in No. 72-394, at 32 n.22.[11] However, even assuming that a negative NAS-NRC report is sufficient in some circumstances to shift the burden to the manufacturer to come forward with the evidence on which he relies, that does not affect the burden of persuasion on summary judgment. The Commissioner retains the burden of showing that the facts alleged by the manufacturer—if true—could not support a finding of substantial evidence of effectiveness.

The regulations involved in the *Hynson, Westcott & Dunning* case are expressly modeled after Rule 56 of the Federal Rules of Civil Procedure. See 35 Fed. Reg. 7251 (1970) (preface to adoption of rules). They permit a hearing to be denied only if the manufacturer's factual claims are facially incapable of meeting the legal test for continued approval—that is, only

> "[*w*]*hen it clearly appears* from the data in the application and from the reasons and factual analysis in the request for the hearing *that there is no genuine and substantial issue of fact* which pre-

[10] Memorandum for Respondents on Petition for Certiorari in No. 72-666, at 4.

[11] The D. C. Circuit noted that the NAS-NRC reports relied upon by the Commissioner in that case were "cryptic and conclusory, without any statement of supporting facts." 466 F.2d at 461. That defect is typical of the reports of the NAS-NRC panels. See, *e.g.*, J.A. 196-97.

> cludes . . . the withdrawal of approval of the application. . . ." 21 C.F.R. § 130.14(b) (emphasis added).

The lower federal courts have upheld these regulations only after construing them to incorporate the basic summary judgment principles discussed above. *Ciba-Geigy Corp.* v. *Richardson*, 446 F.2d 466, 468 (2d Cir. 1971); *USV Pharmaceutical Corp.* v. *Secretary of Health, Education & Welfare*, 466 F.2d 455, 460-61 & n.5 (D.C. Cir. 1972); *Pharmaceutical Mfrs. Ass'n* v. *Richardson*, 318 F. Supp. 301, 311-13 (D. Del. 1970); *cf. Upjohn Co.* v. *Finch*, 422 F.2d 944, 955, 960 (6th Cir. 1970). Indeed, the regulations had their genesis in two federal court decisions which condemned previous attempts by the Commissioner to require a manufacturer to prove the merits of its factual contentions in order to obtain a hearing. *American Home Prods. Corp.* v. *Finch*, 303 F. Supp. 448, 454 (D. Del. 1969); *Upjohn Co.* v. *Finch*, 303 F. Supp. 241, 257-58 (W.D. Mich. 1969).[12]

When the regulations were issued, PMA wrote to the Commissioner, attempting to obtain assurance that he intended to apply the regulations in accord with their apparent recognition that a manufacturer is entitled

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[12] In *American Home*, the Commissioner had revoked his approval of an antibiotic under Section 507 of the Act without a hearing, even though the manufacturer had made factual assertions which the court found were "not 'frivolous,' 'inconsequential' or 'legally insufficient,'" 303 F. Supp. at 454, 456. The court enjoined the Commissioner's action, stating:

> "It appears to this Court that the Commissioner may have made the test of substantial evidence of effectiveness—the showing required to justify continued certification of the drug—the test of whether the [manufacturer] is entitled to a hearing. . . .
>
> "My reading of the *Dyestuffs* case and interpretation of the statutory scheme provided by § 507(f) of the Act indicates that 'reasonable grounds' [for a hearing] should be understood as meritorious, non-frivolous objections, which could most appropriately be resolved finally after a full hearing." *Id.* at 454.

to a hearing on any genuine issue of material fact. PMA's letter posed the question whether, under the regulations, a manufacturer would be granted a hearing if he presented one or more affidavits by qualified experts, summarizing the clinical tests and concluding that some of them met the criteria in the regulations for "adequate and well-controlled" tests and that, either alone or together with other clinical evidence, they sufficiently established the effectiveness of the drug.[13] The Commissioner's answer was noncommittal and unclear.[14] For

[13] The full text of PMA's question was as follows:

"Assume that a party affected by a proposed withdrawal of a new drug application or repeal of an antibiotic regulation presents, in his request for a hearing, one or more affidavits by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved. These affidavits summarize the clinical tests conducted and conclude that some of them meet the criteria set forth in Section 130.12(a) (5) (ii) (*a*) and that, either alone or together with other clinical evidence, they adequately establish the effectiveness of the drug. If you were to disagree as to either point, would you still rule that there is a genuine and substantial issue as to the existence of substantial evidence and, therefore, that a hearing was required?" Letter from C. Joseph Stetler, President, Pharmaceutical Manufacturers Association, to Charles C. Edwards, M.D., Commissioner of Food and Drugs, dated June 3, 1970, attached as Exhibit 5 to the Complaint in *Pharmaceutical Mfrs. Ass'n* v. *Richardson*, Civ. No. 3946 (D. Del., filed July 22, 1970).

[14] The Commissioner responded as follows:

"First, opinion evidence in an affidavit could not provide a basis for determining whether there is substantial evidence derived from adequate and well-controlled clinical investigations. This determination would have to be made upon the basis of an examination of the medical documentation offered. What the regulations require is that the request for a hearing contain a well-organized factual discussion of the available data, in sufficient detail to allow a medical judgment as to the conclusions that may properly be drawn from the data. If the medical documentation contains no substantial evidence, even when accepted at face value, there is no issue of fact for a hearing. But if this factual analysis identifies studies meeting the criteria for adequate and well-controlled studies which appear

that reason, PMA brought suit, arguing that the regulations were invalid if construed to permit the Commissioner to resolve disputed issues of fact as a basis for denying a hearing. *Pharmaceutical Mfrs. Ass'n* v. *Richardson, supra.*

During the oral argument in that suit, counsel for the Commissioner gave the district court the assurances that the Commissioner failed to give in response to PMA's letter. He stated that, under the regulations,

> "where there are legitimate differences of opinion about adherence to those criteria then you have disputed issues of fact which call for a hearing. . . . .
>
> ". . . The problem is and all the problem is that we are dealing here with applications which *fail to show on their face* that they gave attention to these issues." [15]

After receiving these assurances, the district court upheld the regulations on the ground that they followed the principles of Rule 56. The court held that the regulations "simply provide that a request for an evidentiary hearing will be denied *when it clearly appears* that the medical documentation, which the hearing applicant is required to submit, *shows on its face* that there is no

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to support the promotional claims, a hearing may be unnecessary because the claims are proven, or a hearing may be required to test the validity of what has been reported by the investigator and the significance of his observations in providing a basis of fact upon which it could reasonably be concluded by experts that the drug will have the effectiveness claimed for it." Letter from Charles C. Edwards, M.D., Commissioner of Food and Drugs, to C. Joseph Stetler, President, Pharmaceutical Manufacturers Association, dated July 8, 1970, attached as Exhibit 6 to the Complaint in *Pharmaceutical Mfrs. Ass'n* v. *Richardson*, Civ. No. 3946 (D. Del., filed July 22, 1970).

[15] Transcript of Argument at 33, 26, *Pharmaceutical Mfrs. Ass'n* v. *Richardson*, Civ. No. 3946 (D. Del., Oct. 2, 1970) (emphasis added). A copy of the full transcript is being lodged with the Clerk of this Court.

genuine and substantial issue of fact which precludes withdrawal of the new drug approval . . . ." 318 F. Supp. at 312. The court further observed:

> "Of course, if a given request for an evidentiary hearing were to raise an issue of genuine fact within the regulations, and the Commissioner were to misapply the rules, that would be subject to correction by the Courts." *Id.* at 313.

What facts must a manufacturer offer to prove to establish his right to a hearing? Under Section 505(e), the test for continued approval of an NDA is whether there is "substantial evidence" supporting the drug's efficacy. 21 U.S.C. § 355(e). "Substantial evidence" is defined in Section 505(d) to mean

> "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." 21 U.S.C. § 355(d).

Whether the evidence supporting a particular NDA satisfies each element of this definition is a question of fact. See S. REP. No. 1744, 87th Cong., 2d Sess. pt. 2, at 6 (1962).

The Commissioner's regulations elaborate on the statutory definition, setting forth criteria for determining whether an investigation is "adequate and well-controlled." 21 C.F.R. § 130.12(a)(5)(ii). However, virtually all of those criteria are imprecise and judgmental. They call, *inter alia*, for "adequate assurance" that "suitable" subjects were chosen for the study; grouping of subjects "in such a way as to minimize" bias; comparison with a control "in such a fashion as to permit" quantitative evaluation; and determination of whether placebo

effect is "negligible". These are not "bright line" tests whose satisfaction will always be as readily apparent as whether the license applicant in *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192 (1956), already owned five radio stations. Expert opinions may differ about whether any one of the criteria is met in a particular case.[16]

Experts may differ also about whether particular studies form a basis for a conclusion of effectiveness. Indeed, the judgmental nature of these questions is the very reason for the "substantial evidence" test: Congress intended to allow for subjective differences of opinion among qualified experts and to permit a drug to be marketed even though a *minority* of the experts judge that its effectiveness has been appropriately demonstrated.[17] Where the manufacturer offers the opinion of a qualified expert that a certain study or group of studies meets the criteria for an "adequate and well-controlled investigation" and establishes the effectiveness of a product, a genuine factual dispute is presented. That dispute can be resolved only through confrontation and cross-examination at an evidentiary hearing. The Commissioner may not weigh the manufacturer's documentation against the views of his own experts and decide the merits of the

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[16] It is possible to conceive of a situation in which even the "bright line" test involved in *Storer* might give rise to a factual dispute—for example, where the parties disagree whether the license applicant's relationship to an existing station amounts to ownership. However, the five-station rule obviously leaves little room for differences of opinion, and no factual dispute was even alleged to exist in *Storer*. Similarly, in *FPC* v. *Texaco, Inc.*, 377 U.S. 33 (1964), the agency's rules specifically forbade certain price clauses in natural gas contracts, and the companies did not deny that their contracts contained the forbidden clauses. Therefore, the Government's heavy reliance on *Storer* and *Texaco* (Brief for Petitioners in No. 72-394, at 22-24, 26) simply misses the point of those cases.

[17] S. REP. No. 1744, 87th Cong., 2d Sess. 16 (1962); *id.*, pt. 2, at 5-6, 56-58; 108 CONG. REC. 10108 (1962) (remarks of Sen. Hruska); *id.* at 17366 (remarks of Sen. Eastland).

manufacturer's claims as the basis for granting himself summary judgment.[18]

The decision below in the *Hynson, Westcott & Dunning* case correctly set forth and applied these principles. The court of appeals held that the Commissioner's summary judgment in favor of himself could be supported

> "only if it can be fairly said that the clinical tests and medical studies and investigations submitted by the applicant, if credited and accepted, will not support a finding that they provide 'substantial evidence' of effectiveness [under the statute and regulations] . . . .
>
> . . . Manifestly, the applicant does not have to satisfy or convince the Commissioner by his evidence that his product is effective as a predicate for securing his right to a hearing. If that were his burden, a hearing would never be necessary or appropriate." 461 F.2d at 220 (J.A. 178).[19]

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[18] Of course, the necessary content and specificity of the expert's affidavit will depend on the facts of a particular case. The courts in cases under Rule 56 have developed a body of standards governing the adequacy of affidavits for use on summary judgment. See 6 J. MOORE, *supra*, ¶ 56.22.

[19] While the court of appeals' opinion is imprecise at points, we believe that this passage and the opinion as a whole make clear that the court applied the correct test. The Government criticizes the court of appeals for at one point characterizing the issue to be resolved at the hearing as "the effectiveness of Lutrexin." 461 F.2d at 221 (J.A. 180). The Government seizes upon this one phrase to argue that the court disregarded the test of "substantial evidence" as defined in the Act and regulations. Brief for Petitioners in No. 72-394, at 26-27. However, the remainder of the opinion makes clear that the court used the phrase "the effectiveness of Lutrexin" as a shorthand description of the statutory test. The test for approval of an NDA *is* the actual effectiveness (and safety) of a drug, as contrasted to the test for the applicability of the "new drug" provisions, which is *general recognition* of effectiveness (and safety). (See pp. 32-34, *infra*.) The substantial evidence requirement merely defines the type and quantity of evidence on which the determination of effectiveness depends. The Fourth Circuit's opinions in *Hynson, Westcott & Dunning* and

The court examined the materials submitted by Hynson, Westcott & Dunning with its request for a hearing and concluded that they did not clearly show on their face a lack of substantial evidence. *Id.* at 221 (J.A. 179-80).

In its attack on the Fourth Circuit's opinion, the Government blurs the vital distinction between deciding whether there is a factual dispute that necessitates a hearing and deciding the merits of the factual dispute. The Government argues that the court of appeals should have upheld the denial of a hearing because the Commissioner, *ex parte*, had made "a reasonable *determination* that the studies fail to conform to the regulations." (Brief for Petitioners in No. 72-394, at 35 (emphasis added).) But that determination is one that the Commissioner could lawfully make only after a hearing; in making it here he decided the very factual questions that the hearing would address.

This is revealed by the Government's discussion of the reasons given by the Commissioner for rejecting the studies relied upon by Hynson, Westcott & Dunning. (*Id.* at 37-39.) For example, the Commissioner rejected one of the studies for the stated reason that "[t]he historical controls employed are inappropriate" (J.A. 76), even though the regulations permit the use of historical controls (J.A. 488-89) and the manufacturer offered the opinions of several experts that historical controls are the only possible type of control where the life or death of a fetus is involved. (J.A. 33-34, 37, 41, 44, 51, 55, 59.)[20] If the Commissioner disagreed with those experts

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Bentex show that it fully understood these aspects of the statutory scheme.

[20] The Government criticizes the affidavit of Dr. Sadusk, former Medical Director of the FDA, for failing to state whether he considered the studies relied upon by Hynson, Westcott & Dunning to be "well-controlled." The court of appeals apparently misread his affidavit as addressed to that specific question. 461 F.2d at 221

that tests of Lutrexin using historical controls could be "well-controlled," obviously that disagreement framed a factual issue requiring a hearing.

Perhaps recognizing this, the Government now recharacterizes the Commissioner's objection as going to the adequacy rather than the appropriateness of the historical controls. (Brief for Petitioners in No. 72-394, at 38 n. 27.) But the Commissioner's action is no more defensible on that ground. Neither the regulations nor the Commissioner's decision shows in what way the use of historical controls was inadequate. Since the experts performing the studies obviously thought their controls were adequate, that question can be decided only after full exploration through cross-examination at a hearing. If the Commissioner is permitted to decide such disputes *ex parte*, without a hearing, the Government's statement that "formal hearings are not likely to be needed in many instances" (*Id.* at 20 n.15) will certainly prove true.[21]

The Government's argument concerning the standard of review of the Commissioner's denial of a hearing confirms that it believes the Commissioner can *decide* genu-

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(J.A. 180). In fact, the Sadusk affidavit was addressed to the important question of the appropriateness of historical controls in tests of drugs intended to prevent premature labor and threatened abortions. (J.A. 59.) In attacking it, the Government disregards the other affidavits dealing with the specific studies, several of them by the authors of the studies themselves.

[21] Indeed, so far as we are aware, the FDA has not granted a hearing in any case since its "summary judgment" rules were promulgated in 1970.

For a recent example of the lengths to which the FDA will go to avoid holding a hearing, see 38 Fed. Reg. 6305, 6308 (March 8, 1973), denying a request for a hearing and withdrawing approval of Winthrop Laboratories' NDA for Alevaire notwithstanding the submission of seven affidavits of experts concluding that studies relied upon by the manufacturer constituted adequate and well-controlled studies as defined by the FDA's own regulations and proved the effectiveness of the product.

ine disputes on material issues of fact without a hearing, and then invoke this decision to support his determination that there is no need for a hearing. The Government argues that the Commissioner's summary judgment in favor of himself should be upheld if "supported by the evidence." (*Id.* at 34.) However, that is the test to be applied to a finding of fact made on the record of a hearing, not to a summary determination that no genuine issue of fact exists. See Administrative Procedure Act § 10(e), 5 U.S.C. § 706(2)(E). After the Commissioner has heard conflicting scientific testimony, with the benefit of cross-examination,[22] his conclusions are entitled to the judicial deference embodied in a restricted scope of review. However, the question for the Commissioner in determining whether a hearing is needed is simply whether a material factual dispute exists. That question is one of law. *E.g.*, *NLRB* v. *Bata Shoe Co.*, 377 F.2d 821, 826 (4th Cir.), *cert. denied*, 389 U.S. 917 (1967). Once the Commissioner has decided it, "the appellate court in reviewing must determine whether there is any genuine issue of material fact underlying the adjudication." 6 J. MOORE, *supra*, ¶ 56.27[1], at 2973.[23]

Finally, the Government raises the spectre that it may have to hold thousands of hearings, thus bogging down the implementation of its review of the effectiveness of

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[22] The Court of Appeals for the District of Columbia Circuit has recently reaffirmed the "unique potential" of cross-examination "as an 'engine of truth'—the capacity given a diligent and resourceful counsel to expose subdued premises, to pursue evasive witnesses, to 'explore' the whole witness, often traveling unexpected avenues." *International Harvester Co.* v. *Ruckelshaus* (D.C. Cir. No. 72-1517, Feb. 10, 1973), slip op. at 22.

[23] Summarizing the law under Rule 56, Professor Moore further stated: "The trial court cannot draw upon any discretionary power to grant summary judgment where [the] adjudication involves any genuinely disputed issue of material fact." *Id.* at 2976.

pre-1962 drugs. (Brief for Petitioners in No. 72-394, at 19, 30, 35.)[24] There are several answers to this argument. First, faithful application of summary judgment principles will mean no more than that a manufacturer will receive a hearing when it makes a concrete offer of proof on a material factual issue. The Government's fear that summary judgment will never be possible (*id.* at 35) disregards the years of successful use of summary judgment in the federal courts to weed out cases in which no factual dispute really exists. Second, though it would be faster and cheaper for FDA to proceed *ex parte*, Congress in providing for hearings obviously was willing to pay the price of guaranteeing the fairness that only hearings can provide.[25] Finally, the Government greatly exaggerates the size of the problem. In the recent *American Public Health Ass'n* litigation to which the Government refers,[26] the evidence indicated that a substantial majority of the drugs rated less than "effective" by the NAS-NRC panels have been voluntarily removed from the market and that many of the remainder are duplicates of each other, containing the same active ingredient.[27] The

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[24] It is particularly ironic that this "burden" argument is advanced in a group of cases in which the Government is also asking this Court to vest the FDA with new authority to determine whether products are "new drugs" and to obliterate any "grandfather" protection for pre-1962 products, thus sweeping many additional products into the "new drug" regulatory scheme. See Points II and III, *infra*.

[25] This Court has recently noted the constitutional underpinning for that judgment: "While the problem of additional expense must be kept in mind, it does not justify denying a hearing meeting the ordinary standards of due process." *Goldberg* v. *Kelly*, *supra*, 397 U.S. at 261, quoting *Kelly* v. *Wyman*, 294 F. Supp. 893, 901 (S.D. N.Y. 1968).

[26] *American Public Health Ass'n* v. *Veneman*, 349 F. Supp. 1311 (D.D.C. 1972), discussed in Brief for Petitioners in No. 72-394, at 30 n.20.

[27] Affidavit of John G. Adams, Ph.D., attached to Supplemental Memorandum in Support of Motion of Pharmaceutical Manufacturers Association for Leave to Intervene, *American Public*

number of cases requiring hearings can be expected to be a small fraction of the number of drug claims reviewed by the NAS-NRC panels.

In its *Hynson, Westcott & Dunning* decision, the Court of Appeals for the Fourth Circuit correctly set forth and applied the standard for determining whether a hearing must be held before approval of an NDA is withdrawn for lack of substantial evidence of effectiveness. That ruling should be affirmed by this Court.

II. Under the Food, Drug, and Cosmetic Act, the Courts Have Exclusive Jurisdiction, in Enforcement and Declaratory Judgment Actions, to Determine Whether a Product is a "New Drug."

Three of the cases before the Court are declaratory judgment actions brought by drug manufacturers seeking a judicial determination that certain of their products are not "new drugs" as that term is defined in the Act—either because the products are not "new" within the meaning of amended Section 201(p), 21 U.S.C. § 321(p), or because they were exempted from amended Section 201(p) by the "grandfather" provisions of the 1962 Drug Amendments. The Government has challenged the manufacturers' right to have a court make that determination, arguing that the decision is more properly made by the Commissioner, subject to normal judicial review of agency actions.

Health Ass'n v. *Veneman*, Civ. No. 1847-70 (D.D.C., filed Oct. 5, 1972). Specifically, Dr. Adams stated that in a survey of 681 drugs, manufactured by 47 PMA member companies, which had received no "effective" ratings, 428 had already been removed from the market. Thirty-six others had been accepted as "effective" by the FDA for one or more claims based on additional studies. The remaining 217 include only 152 distinct products, with the others being "obvious duplicates representing either different dosage forms or different strengths of the same active ingredient." *Id.* A copy of Dr. Adams' affidavit is being lodged with the Clerk of this Court.

In the *Bentex* case (No. 72-555), the Court of Appeals for the Fourth Circuit upheld the manufacturers' right to obtain a declaratory judgment on the "new drug" status of their products and rejected the Government's argument that FDA has concurrent jurisdiction to decide that question. *Bentex Pharmaceuticals, Inc.* v. *Richardson*, 463 F.2d 363 (4th Cir. 1972) (J.A. 258). The same court followed that ruling in the *USV* case (No. 72-666), decided the next day. *USV Pharmaceutical Corp.* v. *Richardson*, 461 F.2d 223, 226 (4th Cir. 1972) (J.A. 466).[28]

However, the Third Circuit reached the opposite result in No. 72-528. *Ciba Corp.* v. *Richardson*, 463 F.2d 225 (3d Cir. 1972) (J.A. 215). In a *per curiam* opinion which cited no authorities, the Third Circuit held that the question of "new drug" status had been decided *sub silentio* by the FDA when it withdrew approval of Ciba's previously approved NDA and by a court of appeals in upholding the FDA's action. Therefore, the Third Circuit concluded that Ciba was barred from obtaining a declaratory judgment on the question.[29]

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[28] In *USV*, since there has been a trial in the district court and there are now no disputed issues of fact, the Government does not oppose this Court's reaching the legal issues governing the "new drug" status of the products involved. However, it does indicate its disagreement with the Fourth Circuit's ruling, based on *Bentex*, that those issues are for the courts, not FDA, to decide. See Memorandum for Respondents on Petition for Certiorari in No. 72-666 at 6 n.9.

[29] The remaining case before the Court (Nos. 72-394, 72-414) arises from the FDA's withdrawal of approval of an NDA, of which review was obtained directly in the court of appeals. *Hynson, Westcott & Dunning, Inc.* v. *Richardson*, 461 F.2d 215 (4th Cir. 1972) (J.A. 173). In that case, the manufacturer, having previously been refused a declaratory judgment on the status of its product (*Hynson, Westcott & Dunning, Inc.* v. *Finch* (D. Md., Civ. No. 21112, Sept. 16, 1970)), was also refused a hearing before the FDA on its claim of exemption from the "new drug" requirements. PMA believes that the district court's decision refusing to adjudicate the status of Hynson, Westcott & Dunning's product was erroneous.

For the reasons discussed below, we submit that this conflict between the circuits should be resolved in favor of the Fourth Circuit's carefully reasoned construction of the Act in *Bentex*.

As the *Bentex* opinion demonstrates, Congress has struck a balance in the Act between judicial and administrative authority for its implementation. This balance is reflected in the two major amendments of the federal drug laws since the original enactment of the Food and Drug Act of 1906. Act of June 30, 1906, 34 Stat. 768.

The 1906 Act did not provide for any premarketing review of drugs by an administrative agency. It prohibited the interstate sale of adulterated or misbranded drugs, and statutorily defined what acts constituted adulteration and misbranding. *Id.* §§ 7, 8, 34 Stat. 769-71. The agency was assigned the prosecutorial role of proceeding against violators in court.[30] When the Food, Drug, and Cosmetic Act replaced the earlier law in 1938, it carried forward these self-executing prohibitions—triable in the first instance by district courts—and added a requirement of premarketing administrative clearance for "new drugs." It defined "new drugs" as drugs "not generally recognized as safe" by qualified experts. Act of June 25, 1938, § 201(p), 52 Stat. 1041-42. The Act left manufacturers free to market drugs other than "new drugs" without the prior approval or acquiescence of an administrative agency, subject to the judicial sanctions of injunction, seizure, or criminal penalty if they violated any of the Act's commands—including the specific prohibition against marketing a "new drug" without an effective NDA. See Sections 301(d), 302-04, 505(a), 21

[30] Enforcement actions are actually brought in the name of the United States, by the Department of Justice. The administrative agency investigates possible violations and refers cases to the Department for prosecution. The term "prosecutorial role of the agency" is used in this brief to denote the agency's role in instigating enforcement suits.

U.S.C. §§ 331(d), 332-34, 355(a). Except for the FDA's authority to screen "new drugs" before marketing, the function of the agency under the Act remained prosecutorial.

The 1962 Amendments to the Act, which expanded the definition of "new drugs" to include drugs "not generally recognized as safe *and effective*" and elaborated on FDA's controls over "new drugs" under Section 505 of the Act, did not change the balance between the self-executing and the premarketing clearance aspects of the Act. Pub. L. 87-781, §§ 102-04, *amending* Sections 201(p), 505, 21 U.S.C. §§ 321(p), 355. The FDA was given no authority to require premarketing review of products falling outside the expanded "new drug" category or exempted by the "grandfather" provisions.

Where Congress has wanted to give the FDA decision-making authority, it has known how to do it. See, *e.g.*, Sections 401, 403(j), 502(n), 21 U.S.C. §§ 341, 343(j), 352(n). But the Act makes no provision for FDA adjudication of whether a drug being marketed without an approved NDA is a "new drug" for which the manufacturer should have sought premarketing clearance. It contains no authority for administrative proceedings by which the FDA can order the filing of an NDA or order a halt in the marketing of a product that lacks an approved NDA. The FDA is authorized to investigate such a suspected violation of the Act, just as it may investigate a possible violation of the adulteration or misbranding provisions applicable to "new" and "old" drugs alike. Section 702, 21 U.S.C. § 372. It may, in its prosecutorial role, reach a conclusion that a particular product is a "new drug" requiring premarketing approval. But, as the Fourth Circuit observed in *Bentex*,

> "that opinion is not adjudicatory, it is only the basis on which the FDA, as the prosecutor or initiator of either a seizure or injunctive action in the District Court, may invoke the jurisdiction of that

> Court to determine, among other issues, whether the drug challenged is a 'new drug'." 463 F.2d at 370 (J.A. 266).

In fact, enforcement suits under the "new drug" provision commonly present the courts with a disagreement between the FDA and the manufacturer over a product's status as a "new drug." "New drug" status is "an issue that must be and is resolved . . . in practically every injunctive, seizure, or criminal proceeding under the Act." *Bentex, supra*, 463 F.2d at 372 (J.A. 269) (citing cases).

This does not, as the Government asserts, make for an irrational or ineffective legislative scheme. To the contrary, a manufacturer who entertains some doubt about the "new drug" status of his product need not await FDA enforcement action to remove the uncertainty. The FDA's regulations have long provided that a manufacturer may request the FDA to give an informal opinion on the "new drug" status of a product. See 21 C.F.R. § 130.39. The courts have held—and the FDA has conceded—that the FDA's expression of opinion is a sufficiently final "agency action" to permit the manufacturer to sue for a declaratory judgment under *Abbott Laboratories* v. *Gardner*, 387 U.S. 136 (1967). *E.g.*, *AMP, Inc.* v. *Gardner*, 389 F.2d 825, 826 & n.2 (2d Cir.), *cert. denied*, 393 U.S. 825 (1968). Thus, where the manufacturer and the FDA differ on the "new drug" status of a product, each has an orderly way under the Act to obtain an impartial judicial resolution of the issue. Until very recently, the FDA did not resist a manufacturer's declaratory judgment suit on the ground that the agency itself was empowered to adjudicate the issue subject only to limited judicial review. See, *e.g.*, *AMP, Inc.* v. *Gardner*, *supra*; *Durovic* v. *Richardson*, 327 F. Supp. 386 (N.D. Ill. 1971); *Tara Industries, Inc.* v. *Finch*, CCH Food, Drug & Cosm. L. Rptr. ¶ 40,816 (D.D.C. 1970); *Lemmon Pharmacal Co.* v. *Richardson*, 319 F. Supp. 375 (E.D. Pa. 1970); *cf. Merritt Corp.* v. *Folsom*,

165 F. Supp. 418 (D.D.C. 1958) ("new drug" status determined in suit to enjoin further Government seizure actions).

Nor does this scheme make it difficult to enforce effectively the "new drug" provisions of the Act. The manufacturer who markets a drug without an approved NDA does so at his own risk—the considerable risk of seizure, injunction, or even criminal punishment if a court rules in an enforcement suit that he was wrong in believing his product not to be a "new drug."

The Government suggests that the Fourth Circuit's ruling in *Bentex* will "transfer to the courts" an "enormous volume" of litigation (Brief for Petitioners in No. 72-555, at 34, 58), and that such litigation will involve complex technical questions difficult for the courts to decide. (*Id.* at 34, 39, 43, 44, 55-57.) Both suggestions are wrong. The *Bentex* decision does not create any *new* caseload for the courts, because the courts have always been responsible for deciding "new drug" status, either in an enforcement action [31] or in a declaratory judgment suit.[32]

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[31] See, *e.g.*, *United States* v. *Article of Drug . . . Sudden Change*, 409 F.2d 734 (2d Cir. 1969); *United States* v. *Article of Drug . . . Furestrol*, 415 F.2d 390, 392 (5th Cir. 1969) (*per curiam*); *United States* v. *41 Cases . . . Myconox & Ferro-Lac*, 420 F.2d 1126, 1128 (5th Cir. 1970); *United States* v. *Seven Cartons . . . Ferro-Lac*, 424 F.2d 1364, 1365 (7th Cir. 1970); *United States* v. *354 Bulk Cartons . . . Trim Reducing-Aid Cigarettes*, 178 F. Supp. 847, 852-53 (D.N.J. 1959); *United States* v. *Article of Drug . . . Quinaglute*, 268 F. Supp. 245, 248-49 (E.D. Mo. 1967); *United States* v. *Articles of Drug . . . Quick-O-Ver*, 274 F. Supp. 443, 445-46 (D. Md. 1967); *United States* v. *Article of Drug . . . Line Away*, 284 F. Supp. 107, 112-13 (D. Del. 1968), *aff'd on other grounds*, 415 F.2d 369 (3d Cir. 1969); *United States* v. *Article of Drug . . . Magic Secret*, 331 F. Supp. 912, 914-17 (D. Md. 1971); *United States* v. *Article of Drug . . . Excedrin PM*, CCH Food Drug & Cosm. L. Rptr. ¶ 40,486 (E.D.N.Y., No. 70-C-77, Mar. 5, 1971). See also *United States* v. *Allan Drug Corp.*, 357 F.2d 713 (10th Cir.), *cert. denied*, 385 U.S. 899 (1966).

[32] See, *e.g.*, *AMP, Inc.* v. *Gardner*, *supra*; *Durovic* v. *Richardson*, *supra*; *Lemmon Pharmacal Co.* v. *Richardson*, *supra*; *cf. Merritt Corp.* v. *Folsom*, *supra*.

The Government has made no showing that the courts have been burdened with too many cases of either type. As the Fourth Circuit noted, there is nothing novel about judicial resolution of "new drug" status—what is novel is the Commissioner's assertion that he has the power, nowhere conferred by the Act, to adjudicate the need for a manufacturer to file an NDA for a particular product. 463 F.2d at 370-71 (J.A. 266-67).

Also incorrect is the suggestion that determining "new drug" status requires "resolution of technical issues of fact, requiring highly specialized knowledge, training and experience of a kind not ordinarily possessed by judges." (Brief for Petitioners in No. 72-555, at 43.) In making that argument, the Government blurs the distinction between the legal test of "new drug" status (whether a product is "generally recognized" by experts as safe and effective) and the test for approval of an NDA for a "new drug" (whether the drug is safe and effective *in fact*). Determining whether a drug is *actually* safe or effective may require the resolution of difficult scientific questions, and that determination is made by the FDA in the first instance when it passes on an NDA or when it later decides whether to withdraw its approval.[33] But where "new drug" status is the question, "the safety of the products is not what is at issue . . . . The question is whether there is general recognition among qualified experts of the products' safety and effectiveness." *AMP, Inc.* v. *Gardner, supra*, 389 F.2d at

[33] Even the issue of *actual* safety or effectiveness is decided by the courts where the FDA challenges statements of safety or effectiveness in a drug's labeling as a violation of the misbranding provisions of the Act. The courts have not shown any inability to decide that issue when required. See, *e.g.*, *United States* v. *Lanpar Co.*, 293 F. Supp. 147, 151-54 (N.D. Tex. 1968); *United States* v. *354 Bulk Cartons . . . Trim Reducing-Aid Cigarettes, supra*, 178 F. Supp. at 851-52.

831. The courts unanimously recognize this distinction.[34] To decide "new drug" status, a court need only determine the nature of a drug's reputation among persons with relevant expertise, not whether that reputation is scientifically accurate. The courts can readily decide that question on the basis of expert testimony about the drug's reputation. See *United States* v. *Articles of Drug . . . Quick-O-Ver*, *supra*. "General recognition" is, as the court in *Bentex* observed, "manifestly a justiciable issue." 463 F.2d at 372 (J.A. 269).

The Government goes so far as to argue that there is no difference whatever between the test of substantial evidence of effectiveness and the test of general recognition of effectiveness. (Brief for Petitioners in No. 72-555, at 55-57.) We believe that this issue need not be decided by the Court in these cases.[35] Moreover, there is no basis whatever for the Government's remarkable contention. The statutory definition of substantial evidence of effectiveness appears in Section 505(d) of the Act and is explicitly made applicable only to that subsection and

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[34] See, *e.g.*, *United States* v. *Article of Drug . . . Bentex Ulcerine*, 469 F.2d 875, 878-79 (5th Cir. 1972); *United States* v. *Article of Drug . . . Furestrol*, *supra*, 415 F.2d at 392, *aff'g* 294 F. Supp. 1307, 1310-11 (N.D. Ga. 1968); *United States* v. *Article of Drug . . . Excedrin PM*, *supra*, CCH Food, Drug & Cosm. L. Rptr. ¶ 40,486, at 41,226; *United States* v. *Article of Drug . . . Line Away*, *supra*, 284 F. Supp. at 112; *United States* v. *Articles of Drug . . . Quick-O-Ver*, *supra*, 274 F. Supp. at 445-46.

[35] The Government apparently believes that the question is presented in No. 72-414, *Hynson, Westcott & Dunning, Inc.* v. *Weinberger*. (Memorandum for Respondents on Petition for Certiorari in No. 72-414, at 5-7; Brief for Petitioners in No. 72-555, at 57 n.83.) But the question is not addressed in the petitioner's brief, or in the lower courts' opinions, in that case. In any event, if the Court affirms the Fourth Circuit's decision in *Bentex*, holding that the FDA has no authority to determine the "new drug" issue, there would be no occasion to reach this question in the *Hynson, Westcott & Dunning* case.

to Section 505(e).[36] There is nothing in the legislative history of the 1962 Amendments to indicate that Congress intended the substantial evidence test to have a broader application, or that it intended in enacting the new test to obliterate entirely the distinction between "old" and "new" drugs. The Government's position would effectively deprive the careful definition of "new drugs" in Section 201(p) of the Act of any function, and would sweep all drugs under a requirement of proof of effectiveness by "adequate and well-controlled investigations."

The Commissioner, unhappy with the structure of the Act granting him jurisdiction only to approve, disapprove, or withdraw approval of NDAs filed with him, has now attempted to substitute a regulatory system under which manufacturers would have to submit *all* drugs to the FDA for administrative determination of their "new drug" status. His substitute system rests on two assertions: first, that as a matter of law every filing of an NDA raises for the FDA's determination the issue whether the NDA should have been filed at all; and second, that, where an NDA is not filed, Section 5(e) of the Administrative Procedure Act (which authorizes all agencies to issue declaratory orders where necessary "to determine a controversy or remove uncertainty")[37] requires resort to an administrative "declaratory judgment" proceeding before the FDA to determine whether a product is a "new drug." Thus, the "new drug" status of every drug would come before the FDA for adjudication in one way or another.

This jerrybuilt construct falls of its own weight. The filing of an NDA simply does not under the Act place at issue the "new drug" status of the product covered. To the contrary, it indicates that the manufacturer has

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[36] Section 507(h) also applies the substantial evidence definition to certain antibiotics. 21 U.S.C. § 557(h).

[37] 5 U.S.C. § 554(e).

chosen not to seek resolution of the issue.[38] The FDA's regulations nowhere suggest that "new drug" status is an issue to be decided in NDA approval or withdrawal proceedings. And we are aware of no case in which the filing of an NDA has been regarded by either the FDA or a reviewing court as raising the "new drug" issue for decision.[39]

To read Section 5(e) of the APA as transferring the determination of "new drug" status from a judicial to an administrative forum is equally unsound. That section authorizes an agency to decide by declaratory order only questions which it is otherwise authorized to adjudicate on the record of a hearing. *Boston & M.R.R.* v. *United States*, 162 F. Supp. 289, 293-94 (D. Mass.), *appeal dismissed*, 358 U.S. 68 (1958).[40] In this respect, it mir-

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[38] The Fourth Circuit in *Bentex* said that the filing of an NDA is a "concession" of the "new drug" status of a product. 463 F.2d at 371 (J.A. 268). Whatever the court meant by that, we would not agree that such a filing "concedes" anything about what the status of a drug may be years after the filing. Since a drug that is initially "new" may cease to be so by becoming generally recognized as safe and effective, the original filing of an NDA has no bearing on the status of the drug at a later date.

[39] The Government raises the spectre of abuse of the administrative process by a manufacturer who unsuccessfully challenges a withdrawal of NDA approval before the FDA and on review in the court of appeals, and then seeks "to litigate afresh in a district court the question whether the drug involved required an NDA in the first place." Brief for Petitioners in No. 72-555, at 35, 55. This is an illusory problem. If a manufacturer failed to bring a declaratory judgment suit until after the withdrawal of approval was upheld by the court of appeals, that failure might well justify a district court's refusal in its equitable discretion to entertain a request for declaratory judgment.

[40] The Attorney General's Manual on the APA makes this point perfectly clear:

> "This grant of authority to the agencies to issue declaratory orders is limited by the introductory clause of Section 5 so that such declaratory orders are authorized only with respect to matters which are required by statute to be determined 'on

rors the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02, which authorizes the federal courts to issue declaratory judgments but confers no new jurisdiction on them.[41] In both of the cases cited by the Government in which Section 5(e) was invoked, it was conceded that the agency had authority to adjudicate the question it was attempting to decide by declaratory order. *Frozen Food Express* v. *United States*, 351 U.S. 40, 41, 44 (1956); *Red Lion Broadcasting Co.* v. *FCC*, 395 U.S. 367, 372-73 n.3 (1969). As we have shown, the Food, Drug, and Cosmetic Act does not authorize the FDA to adjudicate "new drug" status. Therefore, Section 5(e) is of no help to the Government at all.

The Government's theory that Section 5(e) confers such jurisdiction, moreover, proves too much. It would logically apply not only to the determination of "new drug" status but also to any question under the Act now

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the record after opportunity for an agency hearing.' . . . For example, where an agency is authorized after hearing to issue orders to cease and desist from specified illegal conduct, it may, under Section [5(e)], if it otherwise has jurisdiction, issue a declaratory order declaring whether or not specified facts constitute illegal conduct. On the other hand, while the Securities and Exchange Commission has long issued informal advisory interpretations through its principal officers as to whether a proposed issue of securities would be exempt from the registration requirements of the Securities Act, there is no statutory agency hearing procedure in which this question can be determined; if securities are sold without registration and the Commission believes that registration was required, it can only institute civil or criminal proceedings. Accordingly, Section [5(e)] does not authorize the Commission to issue declaratory orders as to whether particular securities must be registered under the Securities Act." Attorney General's Manual on the Administrative Procedure Act 59 (1947).

The situation of the FDA with respect to questions of "new drug" status is identical to that of the Securities and Exchange Commission in the Attorney General's example.

[41] *E.g.*, *Skelly Oil Co.* v. *Phillips Petroleum Co.*, 339 U.S. 667, 671-72 (1950); see Attorney General's Manual, *supra*, at 59-60.

decided by the courts. The theory would transform the Act from one enforced largely in the courts, with the Government as prosecutor, to one in which every "controversy" or "uncertainty" is decided in an administrative proceeding where the Commissioner is both prosecutor and judge, and where his decisions are conclusive except for limited judicial review. Whatever the merits of such a change as a matter of policy, it can be effected only by an act of Congress.

The patchwork nature of the Government's argument is further demonstrated by its attempt to find authority for judicial review of the declaratory orders on "new drug" status it claims the FDA has authority to make. The Act authorizes review of the Commissioner's disapproval or withdrawal of approval of an NDA in the courts of appeals, § 505(h), 21 U.S.C. § 355(h), but provides for no other appellate review of decisions under Section 505. See *Turkel* v. *FDA*, 334 F.2d 844, 845-46 (6th Cir. 1964), *cert. denied*, 379 U.S. 990 (1965). Thus, declaratory orders on "new drug" status would not be reviewable in the courts of appeals. The Commissioner suggests that this gap can be closed by permitting the *district courts* to review his declaratory orders under the general review provision in the APA. The result would be that the Commissioner's rulings on "new drug" status would be reviewable sometimes in the courts of appeals (when approval of an NDA has been refused or withdrawn) and sometimes in the district courts. There is nothing to indicate that Congress contemplated such an incongruous result.

The Government relies on a number of decisions of this Court to establish the broad proposition that an agency always has implicit authority to adjudicate the question of its own jurisdiction. (See Brief for Petitioners

in No. 72-555, at 57-60.) However, those cases are clearly not in point. In *Ricci* v. *Chicago Mercantile Exchange*, 93 S.Ct. 573 (1973), this Court dealt with a statute containing an express grant of authority to the Commodity Exchange Commission to "adjudicate and remedy" any violation of the statute or regulations under it. Acting on the "premise" that the question before the Court fell within the agency's adjudicatory power, the Court ruled that the agency should be permitted to decide it first. *Id.* at 581-82. The Court was careful to distinguish its earlier decision in *Silver* v. *New York Stock Exchange*, 373 U.S. 341 (1963), where the Court had refused to require judicial deference to an agency which "had no authority to deal with" the question presented. *Id.* at 579-80. Thus, *Ricci* and *Silver* together stand only for the proposition that where an agency has authority to decide a question, the courts will often defer to it to decide the question in the first instance.

Myers v. *Bethlehem Shipbuilding Corp.*, 303 U.S. 41 (1938), and *Marine Engineers Beneficial Ass'n* v. *Interlake S. S. Co.*, 370 U.S. 173 (1962), both involved applications of the National Labor Relations Act, which conferred "exclusive" jurisdiction on the National Labor Relations Board to adjudicate "any unfair labor practice affecting commerce." Act of July 5, 1935, § 10(a), 49 Stat. 453, *as amended*, 29 U.S.C. § 160(a). In *Myers* the Court held that, since the Board was authorized to decide whether commerce is affected in a particular case, subject to judicial review, an employer could not take that question to court before the Board proceedings were completed. In *Interlake*, the Court held that the Board's exclusive jurisdiction to determine what is a "labor organization" within the Act precluded the state courts from entertaining a suit to determine that question at the same time the Board proceedings were going on.

Similarly, in *FPC* v. *Louisiana Power & Light Co.*, 406 U.S. 621 (1972), the FPC had unquestioned authority to determine whether a natural gas system was interstate and therefore subject to federal control, and the agency was conducting proceedings to decide that question. This Court simply held that the federal courts should not determine the question for themselves "when the precise issue . . . is in the process of litigation through procedures originating in the [agency]." *Id.* at 647. In each of these cases, the statute itself gave the agency the authority to decide the question involved. They have no application in this context, where the Act does not.[42]

The Government purports not to argue that the existing jurisdiction of the courts to determine "new drug" status should be cut off, but only that the FDA should be given *concurrent* jurisdiction to decide the issue. In *Bentex* the Government argued in the district court that the Commissioner should be given "primary jurisdiction" and that the declaratory judgment suit should, therefore, be dismissed. The district court rejected that argument, ruling that it has jurisdiction "concurrent" with the FDA; however, it then proceeded to defer to the FDA for an initial determination of "new drug" status. The Government, having failed to appeal the rejection of its primary jurisdiction theory, now acquiesces in the district court's ruling. (Brief for Petitioners in No. 72-555,

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[42] *Oklahoma Press Publishing Co.* v. *Walling*, 327 U.S. 186 (1946), is even farther afield. In that case, the Federal Wage and Hour Administrator was seeking to exercise his authority to investigate possible violations of the Fair Labor Standards Act, 29 U.S.C. §§ 209, 211. Certain corporations being investigated tried to defeat judicial enforcement of subpoenas on the ground that the Act did not apply to them. The Court held that the Administrator was free to *investigate* the question of coverage, in the performance of his job of "searching out violations with a view to securing enforcement of the Act." 327 U.S. at 216. The power of the FDA in its prosecutorial role to investigate the coverage of the "new drug" provisions is not disputed in the cases now before the Court.

at 46 n.76.) But it is clear that there is no functional difference between the primary jurisdiction theory and the district court's notion of concurrent jurisdiction. As the district court's action in *Bentex* demonstrates, deference to the agency under a concurrent jurisdiction rule would be virtually automatic. The result would be to transfer the determination of "new drug" status in all instances from the courts to the FDA. Both the primary and concurrent jurisdiction theories share a common defect: Both ignore the basic fact that "[t]he only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of approval, of a 'new drug' application." *Bentex*, 463 F.2d at 371 (J.A. 267).

The Commissioner may have reason to wish he had the jurisdiction he asserts. As both prosecutor and judge, he could sweep drugs into the "new drug" category subject only to limited appellate review in the courts. Under the Act as Congress wrote it, on the other hand, the Commissioner has the burden of proving in court in an enforcement action that a product falls within the "new drug" provision.[43] The Commissioner is attempting to shift this burden by assigning himself the right of decision and then requiring the manufacturer to convince a reviewing court that the decision is not supported by substantial evidence in the record. Moreover, the Government appears to argue that the Commissioner's decision would be conclusive in a later enforcement proceeding. (Brief for Petitioners in No. 72-555, at 45 n.74.) Not only would that stand the Act on its head, but by shifting

[43] *E.g.*, *Bentex*, 463 F.2d at 371-72 (J.A. 268-69); *United States* v. *Article of Drug . . . Bentex Ulcerine*, *supra*, 469 F.2d at 878-79; *United States* v. *Articles of Drug . . . Quick-O-Ver*, *supra*, 274 F. Supp. at 445-46. FDA officials have recognized that the burden of proof in an enforcement action is on the Government. See *United States* v. *Allan Drug Corp.*, *supra*, 357 F.2d at 718 (quoting statement by HEW Secretary); CHRISTOPHER, CASES & MATERIALS ON FOOD & DRUG LAW 461 (1966) (quoting statement by FDA Deputy Commissioner).

the burden of proof in a criminal enforcement action, it would raise obvious constitutional issues. See *In re Winship*, 397 U.S. 358 (1970).

In sum, as the Fourth Circuit in *Bentex* concluded, the Act gives the Commissioner no authority to adjudicate the "new drug" status of a manufacturer's product. Where the Commissioner believes a manufacturer has wrongly failed to file an NDA, the Act gives him "certain potent judicial remedies, *available exclusively in the District Court.*" [44] The decision of the Fourth Circuit to that effect should be affirmed.

III. The Fourth Circuit Improperly Denied "Grandfather" Protection Under Section 107(c)(4) of the 1962 Drug Amendments to Products Which Were Neither "New" nor Covered by an Effective New Drug Application on the Day Before the Enactment Date of the Amendments.

USV Pharmaceutical Corp. v. *Weinberger*, No. 72-666, and *Hynson, Westcott & Dunning, Inc.* v. *Weinberger*, No. 72-414, raise questions concerning the scope of protection, under the "grandfather" clauses of the 1962 Drug Amendments, P.L. 87-781, 76 Stat. 780, 788-89, afforded to drugs which were no longer "new" drugs on the day before the enactment date of the Amendments but which had previously been covered by effective new drug applications.

Under Section 505(a) of the Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(a), it is unlawful to market a "new drug" unless there is an effective NDA for such drug on file with the FDA. Before the enactment date of the 1962 Drug Amendments, a "new drug" was defined in Section 201(p) of the Act as one

> "not generally recognized, among experts qualified by scientific training and experience to evaluate the

[44] 463 F.2d at 366 (J.A. 260) (emphasis in original).

> safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . ." 52 Stat. 1041 (1938).

The FDA was required under Section 505 to deny or suspend the effectiveness of an application if it appeared that the drug was unsafe or the application incomplete or inaccurate. 52 Stat. 1052-53 (1938).

The Amendments added a requirement of *effectiveness* to the existing requirement of *safety*. This change was reflected in two basic ways. First, the category of "new drugs" subject to the application requirements was expanded to include any drug the safety *and* effectiveness of which is not generally recognized by qualified experts. Section 201(p), 21 U.S.C. § 321(p). Second, Section 505 was amended to require the FDA to deny or withdraw approval of an NDA if it appears that there is not "substantial evidence" that the drug will have the effect claimed for it. Sections 505(d) and (e), 21 U.S.C. §§ 355 (d) and (e).

The Amendments included two grandfather provisions providing exemptions for drugs already on the market. Section 107(c)(3) provides that any drug for which there was an effective NDA on the day before the enactment date[45] may continue to be marketed, even without substantial evidence of effectiveness, so long as approval of the NDA is not withdrawn. And approval of the NDA could not be withdrawn, pursuant to Section 505(e), on the ground of lack of substantial evidence of effectiveness, until two years after the enactment date.

In addition, Section 107(c)(4), which is at issue here, provides a permanent exemption for certain other drugs, so long as there is no change in their recommended uses:

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[45] Section 107(c)(2) provides that an application which was "effective" on the day before the enactment date shall be deemed "approved" by the FDA. And Section 107(c)(3) applies to all drugs whose applications are thereby deemed approved.

> "In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day."

The Fourth Circuit [46] construed Section 107(c)(4) not to exempt drugs which had at any time prior to the day before the enactment date been covered by an effective NDA the approval of which had not been withdrawn pursuant to Section 505(e), 52 Stat. 1053 (1938). It also held that the so-called "me-too" drugs [47] were not covered by the NDAs of other manufacturers' "pioneers" and, thus, that they were entitled to exemption under the statute if they had become old, even though the pioneers were not exempt.[48]

The Government also takes the position that the exemption provided by Section 107(c)(4) does not apply to any drug for which there was *at any time* an effective NDA on file with the FDA, even if the drug had become gen-

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[46] The court articulated its views in the *USV* case, 461 F.2d 223, 226-27 (J.A. 468-70), and it relied without elaboration upon that opinion for its holding on the grandfather issue in the *Hynson, Westcott & Dunning* case. 461 F.2d 215, 219 (J.A. 176).

[47] A "me-too" drug is one which is substantially identical in composition and claims to an NDA'd, "pioneer" drug. 461 F.2d at 228 n.15 (J.A. 470). Such drugs typically were marketed without NDAs because the NDA'd products had become generally recognized as safe.

[48] However, the court held that me-too drugs produced by the manufacturer of the NDA'd drug were covered by the NDA and, thus, were not grandfathered under Section 107(c)(4). 461 F.2d at 229-30 (J.A. 473).

erally recognized as safe before the 1962 Amendments and therefore did not need an NDA, unless the FDA had formally suspended the effectiveness of the NDA.[49] As will be demonstrated below, this position flies in the face of the legislative history of the 1962 Drug Amendments, would make Section 107(c)(4) meaningless, and depends upon a wooden reading of the literal language of that section in isolation, without regard even to the rest of Section 107(c) itself.

Properly construed, Section 107(c)(4) exempts from the amendments to Section 201(p) those drugs which had been commercially marketed prior to the day before the enactment date and had by then become generally recognized as safe for their indicated uses. Such drugs were not "new drugs" on the day before the enactment date, and thus were not then subject to the statutory requirement of an NDA as a condition of lawful marketing. Their NDAs had clearly become obsolete and superfluous.[50] Accordingly, such drugs could not be said to have

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[49] See Memorandum for Respondents in No. 72-666, at 8. The Government parts company with the Fourth Circuit in maintaining that the me-too drugs were covered by the pioneers' NDA's. *Id.* at 9-11.

[50] This was recognized as recently as last year in testimony by the General Counsel of the FDA, who stated that NDA's are "obsolete or inactive" when "the drug has become an old drug." *Hearings on Present Status of Competition in the Pharmaceutical Industry Before the Subcommittee on Monopoly of the Senate Select Committee on Small Business*, 92d Cong., 2d Sess., Part 22, at 8530. Similarly, a commentator has noted:

> "It just doesn't seem to make any sense to argue that such [old] drugs remained 'covered by' their earlier NDA clearance when the manufacturing procedure, formulation, claims, and so forth, could have been (and often were) changed without the necessity of submitting a supplemental NDA unless the change was such that it caused the drug to become again a new drug, and when any newcomer could market the same drug without any NDA clearance." Hagan, *Grandfather Protection Under the Drug Admendments of 1962*, 19 FOOD DRUG COSMETIC L.J. 119, 123 (1964).

been covered by an effective application and, thus, are grandfathered, as to pre-1962 claims, by Section 107(c)(4).[51] These products, of course, are still fully subject to the adulteration and misbranding sections of the statute, so the FDA is assured of ample power to protect the public health.[52]

A. *The Grandfather Clause Must Be Construed in Light of Congress' Basic Intention to Apply the Effectiveness Requirement Only to New Products and New Claims for Old Drugs.*

The legislative history of the 1962 Amendments bearing directly upon Section 107(c)(4) is admittedly sparse. But an examination of the legislative history of the basic effectiveness amendments to which this grandfather provision relates sheds considerable light on its meaning. That history makes it clear that Congress did not intend to subject existing claims for "old" drugs to the new effectiveness requirements.

The amendment to Section 201(p) of the basic Act expanding the definition of "new drug" to include any drug not generally recognized as effective, as well as safe, was included in the original version of the 1962 Drug Amendments, S. 1552. However, when the bill was

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[51] This construction of Section 107(c)(4) obviates resolution of the question of whether the so-called me-too drugs should be deemed to be "covered" by NDAs issued to pioneer products. Because of a divergence of interest among its member companies, PMA expresses no view on the question of whether—if the construction of Section 107(c)(4) urged here is rejected—me-too products can nonetheless qualify for grandfather protection, as USV maintains in No. 72-666.

[52] For example, manufacturers who make extravagant claims for the effectiveness of their products have rendered the products misbranded under Section 502(a) of the Act, 21 U.S.C. § 352(a), and have, therefore, committed a prohibited act subjecting themselves to the full range of enforcement actions under Title III of the Act.

first reported out of the Senate Judiciary Committee on July 19, 1962, this provision was eliminated, and the existing definition of "new drug" was left unchanged. The Committee feared that changing the definition would have the effect of causing old, "established drugs," which were generally recognized as safe and, thus, not "new drugs," to be deemed "new drugs" required to go through the new drug clearance procedure. S. REP. NO. 1744, 87th Cong., 2d Sess. 17 (1962).

Several members of the Committee, including the bill's sponsor, Senator Kefauver, dissented from this decision and argued that the definition of a "new drug" should be amended to include a requirement of effectiveness. Such a change was necessary, they reasoned, in order that each *new claim* for drugs lawfully marketed would be subject to the effectiveness requirement. See *id.* at 34 (separate statement of Sens. Kefauver, Carroll, Dodd, Hart and Long). In other words, the dissenters did not take issue with the Committee's objective of exempting old drugs from the effectiveness requirement, except in the case of new claims. See also remarks of Senator Kefauver, 108 CONG. REC. 10278 (1962).[53]

Ultimately, Senator Kefauver prevailed, and the definition of "new drug" was changed in amendments to the bill which were reported out of the Judiciary Committee on August 21, 1962. The Committee Report which accompanied the amendments described the change as intended to eliminate ambiguity concerning "the circumstances and extent to which a new claim or change of claim" could be made without supporting evidence of effectiveness submitted to the FDA. S. REP. NO. 1744, 87th Cong., 2d Sess.

[53] The focus upon new claims for existing drugs was reflected later in the legislative history as well. See, *e.g.*, remarks of Senator Kefauver, 108 CONG. REC. 22045 (1962) (arguing that the definition of "new drugs" should me amended to close the "loophole" which would permit the manufacturer of an existing drug to avoid the new drug application procedure for new claims).

pt. 2, at 5 (1962). And Senator Eastland, chairman of the Judiciary Committee, introduced the new amendments with a lengthy discussion of the bill's provisions on the floor of the Senate:

> "The term 'new drug' is presently defined as one not generally recognized to be safe for the claimed uses or one, which while so recognized, has not been used for a material time or to a material extent for such uses. The bill would expand this definition so that the term 'new drug' would also include [a drug] not generally recognized to be effective for the claimed uses or one, which while so recognized, has not been used for a material time or to a material extent for such uses. Thus, *every brandnew product, and every new claim for an existing product*, would be subject to the tests and procedures established in section 505 of the act." 108 CONG. REC. 17366 (1962) (emphasis added).

The amendments reported out of the Judiciary Committee also included, for the first time, the grandfather provisions of Section 107(c). Section 107(c)(3) provided a limited, two-year grace period for drugs covered by effective NDAs, and Section 107(c)(4) provided a permanent exemption to certain other drugs. Evidently, this latter provision was included in the bill in order that the change in the "new drug" definition might serve its proponents' purposes without at the same time ignoring the repeated concern of Congress that established old drugs should not be required to go through the new drug procedure and demonstrate "substantial evidence" of effectiveness for existing claims. Senator Kefauver had anticipated the inclusion of this grandfather provision two weeks earlier. In arguing for the new definition of "new drugs," he was careful to note: "[T]he amendment to the definition of 'new drugs' would not require resubmission of all the thousands of 'new drugs' hitherto cleared for

the market in order to obtain reclearance for efficacy." 108 CONG. REC. 15696 (1962).[54]

In sum, the new definition of "new drugs" was intended only to assure that new products and new claims for existing old drugs would require substantial evidence of effectiveness. Neither the proponents nor the opponents of this change sought to require old drugs to demonstrate efficacy for existing claims as a prerequisite to continued marketing. Section 107(c)(4), which provides an exemption from the change in the definition of "new drugs," must be construed in furtherance of this purpose. The construction of Section 107(c)(4) urged by the Government, which would have the result of causing the thousands of drugs already lawfully on the market and generally recognized as safe to be subject to the amended new drug clearance procedure, flies in the face of this clear and overriding legislative purpose.

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[54] In light of this repeated concern in the legislative history that not all drugs previously on the market should be required to demonstrate effectiveness for existing claims, the language in the Conference Report, H.R. REP. No. 2526, 87th Cong., 2d Sess. 23 (1962), that Section 107(c)(4) applies to drugs that have "never previously been subject to the new-drug procedure" should properly be construed as a partial description of the class of drugs grandfathered by the provision, and not as a limitation upon the scope of the provision. Nothing in the quoted language or the history of the section suggests that Congress intended it to be such a limitation. Moreover, if construed as a limitation, the language proves too much, for it would be inconsistent with the concession by both the Fourth Circuit (461 F.2d at 219, 227 (J.A. 176, 469)) and the Government (Memorandum for Respondents on Petition for Certiorari in No. 72-666, at 8) that, under some circumstances, an effective NDA could have ceased to be effective before 1962. See 52 Stat. 1053 (1938). What is more, as will be seen below, such a construction, when combined with the Government's position that me-too drugs are covered by NDAs for pioneer products, would render Section 107(c)(4) entirely meaningless.

B. *The Construction Urged by the Government Would Render Section 107(c)(4) Meaningless.*

The reading of Section 107(c)(4) urged by the Government not only is fundamentally inconsistent with the legislative history, but also would result in a strained and senseless construction of the statute. Indeed, in the last analysis, the Government's construction would as a practical matter render Section 107(c)(4) entirely meaningless.

All drugs which were sold prior to 1938 are exempted from the new drug application procedure by Section 201(p) of the Act, 21 U.S.C. § 321(p). Since a drug could not become an old drug without having been marketed for a time (Section 201(p)(2)), every drug first marketed between 1938 and 1962 must have at some time been a "new drug." See 52 Stat. 1041 (1938). And no such drug could lawfully have been marketed without an effective NDA. 52 Stat. 1052 (1938). If, as the Government maintains, an NDA which is once effective is always effective and if the so-called me-too drugs are deemed to be "covered" by the NDA for the pioneer drug, then every drug which was at any time "new" would have been covered by an effective application on the day before the enactment date.[55] Thus, other than those drugs already exempted by Section 201(p), no drug would qualify for exemption under Section 107(c)(4),

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[55] In spite of the fact that both the Fourth Circuit in *USV* (461 F.2d at 226 (J.A. 468)) and the Government (see Memorandum for Respondents in No. 72-666, at 7-8) purport to recognize that a "new drug" may have become old when, as a result of widespread experience and use, it became generally recognized as safe, their claim now—that a drug remained covered by an effective NDA no matter how obsolete or superfluous the NDA may have become—amounts to saying that every drug which was *once* "new" before the enactment date of the Amendments, and thus subject to the NDA requirements, was *always* "new."

and that provision would serve no purpose at all.[56] This Court should not construe Section 107(c)(4) in such a way as to render it entirely meaningless, when a sensible alternative construction is available. See, *e.g.*, *Rosado* v. *Wyman*, 397 U.S. 397, 415 (1970).

In order to avoid having to defend a construction of the statute which would render Section 107(c)(4) entirely meaningless, the Government argues that a drug may have ceased to be covered by an effective NDA if the effectiveness of the NDA had been formally suspended by the FDA pursuant to Section 505(e). See Memorandum for Respondents on Petition for Certiorari in No. 72-666, at 8. The Fourth Circuit took the same position in the *USV* decision. 461 F.2d at 227 (J.A. 469). But Section 505(e) simply required the FDA to suspend the effectiveness of an NDA when it found that the drug was unsafe. On its face, it is clear that section was intended, not to restrict the circumstances under which an NDA may become ineffective, but only to limit the circumstances under which a manufacturer could have required continued FDA approval. In construing the statute as precluding termination of the effectiveness of an NDA under any other circumstances, the Government would have this Court believe that Congress intended suspension of effectiveness of an NDA for lack of safety to be a prereq-

[56] Surely, Congress did not intend to exempt only those drugs which were never covered by effective NDAs and yet were marketed unlawfully, and we assume the Government does not suggest that Section 107(c)(4) grandfathers such drugs.

The Fourth Circuit's view of Section 107(c)(4) would preserve a limited purpose for it—to grandfather me-too products that were generally recognized as safe on the day before the enactment date of the Amendments. However, nothing in the legislative history of the statute suggests that this grandfather provision was intended to apply *only* to those drugs. This Court can avoid this distinction between pioneers and me-toos, without reaching the me-too question or prejudicing the status of me-too drugs under the grandfather clause, by holding that the Section 107(c)(4) exemption applies to all old drugs, pioneers and me-toos as well.

uisite to exemption under the grandfather clause. Surely Congress could not have intended such an absurd result.

Thus, the position of the Government would compel an irrational construction of Section 107(c)(4): it would render that grandfather provision substantially useless.

C. *The Fourth Circuit Erred in Relying upon the "Surplusage" Argument.*

In its *USV* decision, the Fourth Circuit rejected, for one reason only, the argument advanced here that an old drug could not be "covered by an effective" application and that Section 107(c)(4) therefore served to exempt existing claims for old drugs from the amended "new drug" definition. "The difficulty with this argument, plausible though it may be," reasoned the court, "is that it would make surplusage of requirement (C) in the exemption statute." 461 F.2d at 227 (J.A. 469). In other words, the Fourth Circuit maintained that if every drug which satisfied clause (B) of Section 107(c)(4) (*i.e.*, every old drug) thereby met the requirements of clause (C) (*i.e.*, ceased to be covered by an effective NDA), then clause (C) would be redundant, mere surplusage. The view that the construction of Section 107(c)(4) adopted by the Fourth Circuit was necessary in order to prevent clause (C)'s being unnecessary was the *only* basis for the court's holding.

Although this reasoning has some superficial appeal when Section 107(c)(4) is read in isolation, its plausibility as a basis for decision vanishes when that provision is read in conjunction with the remainder of Section 107 and, in particular, Section 107(c)(3). For when those two provisions are read together, it is apparent that clause (C) is unnecessary surplusage under the Fourth Circuit's and the Government's construction of Section 107

(c) (4)—based upon the premise that a no longer "new" drug may still be covered by an effective NDA—as well as the construction urged here. Under the circumstances, this Court should disregard the surplusage issue and adopt that construction which gives the most sensible meaning to Section 107(c) (4) as a whole.

Section 107(c) (3) provides, in effect, that a drug whose application is deemed approved, *i.e.*, one whose application was effective on the day before the enactment date of the Amendments, may have its application withdrawn after two years on account of inefficacy. Without clause (C), Section 107(c) (4) provides that drugs which were "old" on the day before the enactment date are forever exempted from the requirement of showing efficacy as to existing claims. Obviously, Section 107(c) (4), *even without clause (C)*, could apply only to old drugs not covered by an effective NDA, because Section 107(c) (3) makes it clear that all drugs covered by an effective NDA are not permanently grandfathered. If Section 107(c) (4), even without clause (C), were read to permanently grandfather old drugs covered by effective NDAs, then Sections 107(c) (3) and (4), read together, would stand for the inconsistent propositions that a drug which is old but which is covered by an effective NDA (1) may have its new drug application withdrawn on grounds of inefficacy after two years (§ 107(c) (3)), and (2) is exempt from the efficacy requirements of the Act (§ 107(c) (4)). In order to avoid this patent contradiction, Section 107(c) (4), even without clause (C), would have to be read to apply only to drugs not covered by effective applications. Thus, the purpose assigned to clause (C) by the Government and the Fourth Circuit—distinguishing old drugs covered by effective applications from those not so covered—is actually served by Section 107(c) (3). In short, even under the Fourth

Circuit's and the Government's view, clause (C) is superfluous.[57]

The error in the court's analysis stems from its asking what purpose clause (C) serves, given clauses (A) and (B). The more logical way to interpret Section 107(c)(4) is to begin at the end of Section 107(c)(3). Section 107(c)(3) defines the grandfather protection for drugs covered by effective applications. What is left are drugs not covered. Thus, analytically, clause (C) serves as a restatement in Section 107(c)(4) of the relevant aspect of Section 107(c)(3). The question the Fourth Circuit should have asked is, given 107(c)(3) and 107(c)(4)(C), why include 107(c)(4)(A) and (B). The reason, obviously, is to prevent exempting from the efficacy requirements drugs which were not covered by an effective application but had not become generally recognized as safe through commercial use.

In sum, the surplusage argument upon which the Fourth Circuit relied provides no basis for distinguishing the construction urged here from that argued by the Government. Since Section 107(c)(3) governs all drugs that are covered by effective NDAs, there is no construction of Section 107(c)(4) under which clause (C) is not surplusage. This Court should therefore construe Section 107(c)(4) in light of its legislative purpose and the statutory

[57] The Government might attempt to avoid this dilemma by arguing that Section 107(c)(3) applies, not to all drugs with effective applications, but only to "new drugs" with effective applications. Given this reading of Section 107(c)(3), the class of drugs which meet the requirements of Section 107(c)(4)(B) might include old drugs covered and those not covered, apparently making (C) necessary. The trouble with this argument, however, is that, since Section 107(c)(3) does not refer to "new" or old drugs, the narrowing gloss on 107(c)(3)—that it applies only to "new drugs"—would depend upon the premise that a drug with an effective application *must* be "new", *i.e.*, that an old drug cannot be covered by an effective NDA. Thus, such an argument would depend upon the very premise the Government rejects.

scheme as a whole. Congress did not intend its 1962 Amendments to apply to existing claims for old drugs, nor did it write Section 107(c)(4) with no purpose in mind. That provision should be construed to exempt from the new "new drug" definition all drugs which had become generally recognized as safe by the day before the enactment date of the Amendments, because such drugs cannot in any meaningful sense be said to have been "covered by an effective" NDA at that point.[58] Accordingly, the decision of the Fourth Circuit denying grandfather status to such drugs should be reversed.

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[58] Such a holding would make unnecessary the Court's deciding separately the status under the grandfather provisions of drugs whose NDAs had been withdrawn by action of the manufacturer. See Brief for Petitioner in No. 72-666, at 68-76.

CONCLUSION

For the reasons stated above, the judgment of the court of appeals in the *Hynson, Westcott & Dunning* case (Nos. 72-397 and 72-414) should be affirmed insofar as the court held that the FDA could not withdraw approval of the manufacturer's NDA without providing a hearing on the question of substantial evidence of effectiveness; the judgment of the court of appeals in No. 72-528 should be reversed; the judgment of the court of appeals in No. 72-555 should be affirmed; and the judgment of the court of appeals in No. 72-666 should be reversed.

Respectfully submitted,

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Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-634

CASPAR W. WEINBERGER, ET AL., *Petitioners*

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, *Respondent*

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

No. 72-414

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, *Petitioner*

v.

CASPAR W. WEINBERGER, ET AL., *Respondents*

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

No. 72-595

CIBA CORPORATION, *Petitioner*

v.

CASPAR W. WEINBERGER, ET AL., *Respondents*

On Writ of Certiorari to the United States Court of Appeals for the Third Circuit

No. 72-596

CASPAR W. WEINBERGER, ET AL., *Petitioners*

v.

BENTEX PHARMACEUTICALS, INC., ET AL., *Respondents*

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

No. 72-636

USV PHARMACEUTICAL CORPORATION, *Petitioner*

v.

CASPAR W. WEINBERGER, ET AL., *Respondents*

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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H. R. Rep. No. 2526, 87th Cong., 2d Sess. (1962) 53, 54
Project, Federal Administrative Law Developments—1971, 1972 Duke L. J. 115 49
Shapiro, The Choice of Rule Making or Adjudication in the Development of Administrative Policy, 78 Harv. L. Rev. 921 (1965) 38
S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess. (1962) 52, 53, 55, 61, 68
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Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-394

CASPAR W. WEINBERGER, ET AL., *Petitioners*

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, *Respondent*

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

---

No. 72-414

HYNSON, WESTCOTT AND DUNNING, INCORPORATED, *Petitioner*

v.

CASPAR W. WEINBERGER, ET AL., *Respondents*

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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No. 72-528

CIBA CORPORATION, *Petitioner*

v.

CASPAR W. WEINBERGER, ET AL., *Respondents*

On Writ of Certiorari to the United States Court of Appeals for the Third Circuit

---

No. 72-555

CASPAR W. WEINBERGER, ET AL., *Petitioners*

v.

BENTEX PHARMACEUTICALS, INC., ET AL., *Respondents*

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

---

No. 72-666

USV PHARMACEUTICAL CORPORATION, *Petitioner*

v.

CASPAR W. WEINBERGER, ET AL., *Respondents*

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

---

MOTION FOR LEAVE TO FILE BRIEF AMICUS CURIAE ON BEHALF OF THE PROPRIETARY ASSOCIATION

The Proprietary Association, pursuant to Rule 42 of the Rules of this Court, hereby respectfully moves this Court for leave to file a brief *amicus curiae* in these cases, treating the issues raised therein and opposing the position of the Government petitioners in *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.*, No. 72-555 (hereafter *"Bentex"*). Written consent for the filing of such brief has been obtained from the Solicitor General and from the attorneys for all parties involved except Hynson, Westcott and Dunning, Incorporated, whose attorneys have withheld consent.

Movant, The Proprietary Association, is a 92-year-old national trade association located at 1700 Pennsylvania Avenue, N.W., Washington, D. C. 20006, whose 82 active member companies manufacture and distribute most of the Nation's supply of proprietary "over-the-counter" medicinal preparations ("OTC drugs"). OTC drugs are those which can be legally dispensed without a prescription; "proprietary" OTC drugs are those which are promoted and sold directly to the public; and "pharmaceutical" or "ethical" OTC drugs are those which are sold without prescription but promoted only to members of the health professions.

These cases present the question, as stated in the Government's brief in *Bentex:* "Whether the Food and Drug Administration has jurisdiction to determine initially whether a product is a 'new drug' which must be administratively approved as safe and effective before it can be sold in commerce." Brief for Petitioners, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.*, No. 72-555, p. 2. Others of the cases here consolidated involve related questions.

The Court's decision on these issues will so substantially and directly affect Movant's members in the con-

duct of their business of manufacturing and distributing OTC drugs as to justify the Court's granting leave to file a brief *amicus curiae.*

Moreover, in its brief in *Bentex,* the Government refers to the Food and Drug Administration's current regulatory program for the review of OTC drugs. It describes this program adopted in May 1972 (37 Fed. Reg. 9464) as follows:

> "... a procedure for determining in substantive rule making, by therapeutic class, whether particular OTC products not covered by NDAs are generally recognized as safe and effective and not misbranded, under the standards of the Act. The procedure involves the establishment of independent expert panels for different categories of OTC drugs (e.g., antacids, laxatives, analgesics), which would review all available data (including any that manufacturers, consumer groups, or others wish to submit) and prepare monographs prescribing drug composition, labeling, and manufacturing controls. Products conforming to the monograph-rule will not be considered to be 'new drugs' requiring an NDA or to be misbranded." *Id.* at pp. 24-25.

By formal comments filed with the Commissioner of Food and Drugs on March 4, 1972, The Proprietary Association objected to the above-described program as later adopted in May 1972. It was and continues to be the position of The Proprietary Association that the FDA does not have statutory authority to issue substantive regulations, having the force of law, as contemplated in the OTC review program. During the time since the adoption of the program The Proprietary Association has co-operated fully in the scientific review, but has carefully preserved its right to con-

test in an appropriate judicial proceeding the legality of the FDA's issuance of a final monograph as a binding regulation.

The Government now apparently seeks, through its brief in No. 72-555, to obtain a premature review by this Court of the validity of its OTC regulations. Its brief includes the following comments:

> "Moreover, the implications of the decision below extend beyond the area of prescription drugs involved in the present case. The agency's current program to review the over-the-counter drugs (see pp. 24-25, *supra*) would also be undermined by the court of appeals' rationale, since the agency would have no power to determine definitively, subject to judicial review, standards by which hundreds of thousands of drugs for which no NDA is in effect may be classified as 'new drugs' or not. The agency would be required to pursue these products throughout the courts of the Nation in innumerable trials considering *de novo* issues that are best suited to administrative resolution and that may, indeed, already have been given careful consideration in administrative proceedings. The decision of the court of appeals would thus leave the agency virtually impotent to deal effectively with the vast task of implementing the 1962 amendments." *Id.* at pp. 36-37.

The Government's effort to bring before the Court its current regulatory effort regarding OTC drugs provides a controlling reason for the Court to grant The Proprietary Association leave to file an *amicus* brief. The Government raises matters which go far beyond the individual interests of the parties now before the Court in these cases. Those parties will necessarily concentrate on the particular facts and issues in their individual cases. We believe that a brief *amicus*

curiae on behalf of The Proprietary Association can assist the Court in resolving the issues now before it and contribute to a more thorough understanding of the profound impact which these decisions will have on both the prescription and the proprietary industries.

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Supreme Court of the United States

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BRIEF AMICUS CURIAE ON BEHALF OF THE PROPRIETARY ASSOCIATION

OPINIONS BELOW

In No. 72-394, *Weinberger* v. *Hynson, Westcott and Dunning, Incorporated,* and No. 72-414, *Hynson, Westcott and Dunning, Incorporated* v. *Weinberger* (hereafter *"Hynson"*), the opinion of the Court of Appeals, captioned *Hynson, Westcott and Dunning, Inc.* v. *Richardson,* is reported at 461 F.2d 215 (4th Cir. 1972). Joint App. 258-270. The opinion of the District Court is not officially reported. Joint App. 251-258.

In No. 72-528, *CIBA Corporation* v. *Weinberger* (hereafter *"CIBA"*), the opinion of the Court of Appeals, captioned *CIBA Corporation* v. *Richardson,* is reported at 463 F.2d 225 (3d Cir. 1972). Joint App. 215-216. The opinion of the District Court was delivered orally and not reported. Joint App. 208-214.

In No. 72-555, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.* (hereafter "Bentex"), the opinion of the Court of Appeals, captioned *Bentex Pharmaceuticals, Inc., et al.* v. *Richardson,* is reported at 463 F.2d 363 (4th Cir. 1972). Joint App. 258-270. The opinion of the District Court is not officially reported. Joint App. 251-258.

In No. 72-666, *USV Pharmaceutical Corporation* v. *Weinberger* (hereafter "USV"), the opinion of the Court of Appeals, captioned *USV Pharmaceutical Corporation* v. *Richardson,* is reported at 461 F.2d 223 (4th Cir. 1972). Joint App. 466-473. The opinion of the District Court is not officially reported, but is reprinted at CCH Food Drug Cos. L. Rep. ¶ 40-489. Joint App. 463-466.

QUESTIONS PRESENTED

Four basic questions are presented by these consolidated cases, one of which involves subsidiary questions which it may be helpful to state explicitly:

(1) Does the Food and Drug Administration ("the FDA") have statutory authority to make a legally binding determination as to whether a drug which has never been the subject of a New Drug Application ("NDA") is a "new drug," as that term is defined in the Federal Food, Drug, and Cosmetic Act? (*Bentex*)

(2) Does Section 107(c)(4) of the Drug Amendments of 1962 give the FDA indirect authority to make a binding administrative determination of the right of a manufacturer to continue to market a drug which has never been the subject of a New Drug Application, by withdrawing its approval of a New Drug Application covering a different but similar drug? (*Bentex* and *USV*)

(3) Does Section 107(c) of the Drug Amendments of 1962 exempt a drug from administrative proceedings to withdraw approval of the NDA covering such drug? (*Hynson*)

(4) If a drug which was once a "new drug" and was originally marketed pursuant to an NDA becomes "generally recognized as safe and effective," does it cease to be a "new drug" as defined in the Act? (*Hynson* and *CIBA*) If so, two subsidiary questions are presented:

(A) Does general recognition of a drug's safety and effectiveness terminate the FDA's au-

thority to withdraw its prior approval of the NDA covering that drug? (*Hynson*)

(B) After the FDA has issued a final order withdrawing its prior approval of an NDA, can the manufacturer continue to market the drug, if it is "generally recognized as safe and effective"? (*CIBA*)

STATEMENT

I. The Relevant Statutory Provisions

A. The "New Drug" Provisions

The Federal Food, Drug, and Cosmetic Act of 1938 ("the Act") replaced the Food and Drugs Act of 1906. A major change made by the 1938 Act was to require pre-marketing clearance by the FDA.[1] However, such pre-clearance was made applicable only to a "new drug," and the FDA's authority was originally limited to a determination of safety. Prior to its amendment in 1962 the Act prohibited the introduction into interstate commerce of any new drug unless an application was "effective with respect to such drug." It provided that such application would "become effective" on the 60th day after it was filed unless the FDA issued a notice postponing the effective date for up to 180 days or issued "an order refusing to permit the appli-

[1] The authority and responsibility under the 1906 and 1938 Acts were originally vested in the Secretary of Agriculture. The functions of the Secretary of Agriculture under the Act were assigned to the Food and Drug Administration, which was transferred in 1940 to the Federal Security Agency, and in 1953 to the Department of Health, Education, and Welfare. While the Act speaks in terms of "the Secretary," the Secretary of the latter department has delegated his authority under the Act to the Commissioner of Food and Drugs. 21 C.F.R. § 2.120; 21 U.S.C. § 321 note (1970). We use "the Commissioner" and "the FDA" as synonymous terms.

cation to become effective." § 505 of the Federal Food, Drug, and Cosmetic Act of 1938, 52 Stat. 1052; Joint App. 483-484.

The Act was amended in 1962 to require the FDA to determine that a "new drug" is effective as well as safe, and to require an NDA to be affirmatively approved rather than "becoming effective" unless refused.[2] The Act prohibits the introduction into interstate commerce of any "new drug" unless the FDA has approved an NDA filed pursuant to the Act. §§ 301(d) and 505, 21 U.S.C. §§ 331(d) and 355. A violation of this provision carries criminal penalties of imprisonment for not more than one year or a fine of not more than $1,000, or both. § 303(a), 21 U.S.C. § 333(a). Such violations may be restrained in an action brought in any U.S. District Court, and a drug introduced into interstate commerce in violation of Section 505 may be seized and condemned in an action filed in the U.S. District Court for the district where such drug is found. §§ 302(a) and 304(a), 21 U.S.C. §§ 332(a) and 334(a).

Section 201(p) defines the term "new drug" to mean: "Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety *and effectiveness* of drugs, as safe *and effective* for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . ," and "which has not . . . been used to a material extent or for a material time . . . ." 21 U.S.C.

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[2] Section 107(c)(2) of the 1962 Amendments provides that a New Drug Application which was "effective" under the 1938 Act on the enactment date of the amendments shall be deemed to be an application "approved" under the Act as amended. Public Law 87-781, 76 Stat. 788-789, 21 U.S.C. § 321 note (1970); Joint App. 481-482.

§ 321(p). The words in italics were added by the 1962 Amendments. In essence, as relevant to the issues presented in these cases, if a drug is "generally recognized . . . as safe and effective," it is not a "new drug" and the provisions of the statute requiring FDA clearance of "new drugs" do not apply.

However, certain drugs even if *not* generally recognized as both safe and effective are still not "new drugs," because of the "grandfather" provisions contained in the original Act and in the 1962 Amendments. Section 201(p)(1) provides further that "a drug not so recognized [as safe and effective] shall not be deemed to be a 'new drug' if at any time prior to the enactment of this Act [on June 25, 1938] it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time [*i.e.,* before June 25, 1938] its labeling contained the same representations concerning the conditions of its use. . . ." Furthermore, a drug which is not generally recognized as effective is not a "new drug" if on the day immediately preceding the date of enactment of the 1962 Amendments, October 9, 1962, it (A) was commercially used or sold in the United States, (B) was not a new drug as defined by the Act as then in force, *i.e.,* was generally recognized as safe, and (C) was not covered by an effective New Drug Application—"when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug" on October 9, 1962. The 1962 Amendments provided that the amended definition of a "new drug," requiring that a drug be generally recognized as effective to avoid "new drug" status, should not apply to a drug meeting the foregoing requirements. § 107(e)(4) of P.L. 87-781, 76 Stat. 788, 21 U.S.C. § 321 note; Joint App. 482.

Thus, three categories of drugs are not "new drugs" and therefore may be marketed without prior clearance and approval by the FDA:

(1) a pre-1938 drug, the labeling of which still contains the same representations concerning its use; and

(2) a pre-1962 drug which was generally recognized as safe and not covered by an effective NDA in 1962, the labeling of which still contains the same representations concerning its use;

(3) a drug which is generally recognized as safe and effective after it has been used to a material extent or for a material length of time.

It should be noted that in each case whether a drug fits one of these three excluded categories involves questions of fact with respect to the particular drug.[3]

B. The "Misbranding" Provisions

The Act likewise prohibits the introduction or delivery for introduction into interstate commerce of any drug that is "misbranded." § 301(a), 21 U.S.C. § 331 (a). A violation of this provision also carries criminal penalties of imprisonment for not more than one year or a fine of $1,000, or both. § 303(a), 21 U.S.C. § 333(a). Such violation may be restrained in an action brought in any U.S. District Court, and a misbranded drug which is introduced into interstate com-

[3] Under a separate paragraph of the "grandfather" clause in the 1962 Amendments, "new drugs" for which an NDA was "effective" on the enactment date of the amendments were granted a two-year moratorium from withdrawal of approval of the NDA under § 505(e) for lack of effectiveness. § 107(c)(3) of P.L. 87-781, 76 Stat. 788, 21 U.S.C. § 321 note; Joint App. 481.

merce or held for sale after interstate shipment may be seized and condemned in an action filed in the U.S. District Court for any district where such drug is found. §§ 302(a) and 304(a), 21 U.S.C. §§ 332(a) and 334(a).

Section 502 provides that a drug shall be deemed to be "misbranded" (1) if its labeling is false or misleading (§ 502(a)), (2) if its labeling does not bear adequate directions for use and adequate warnings as are necessary for the protection of the user (§ 502(f)), or (3) if it is dangerous to health when used in the dosage, with the frequency, or for the duration recommended in the labeling (§ 502(j))—as well as under a number of other circumstances not relevant here. 21 U.S.C. § 352. It should again be noted that whether a drug is misbranded depends upon factual questions with respect to the truth and adequacy of the labeling of the particular drug.

The statutory sanctions against misbranded drugs are applicable by their terms to any "drug," and make no distinction as to whether the drug involved is a pre-1938 drug, a pre-1962 drug which is generally recognized as safe, a drug which is generally recognized as safe and effective, or a "new drug." However, as discussed *infra,* pp. 60-61, there are alternative administrative sanctions available to deal with false and misleading labeling of an NDA'ed drug.

C. Enforcement of the Statutory Provisions

The Act clearly contemplates and authorizes administrative enforcement of its provisions with respect to a "new drug" upon the filing of a New Drug Application. Section 505(b), 21 U.S.C. § 355(b), provides that an application to market a "new drug" shall be filed

with the Secretary (by delegation, the Commissioner of Food and Drugs), and specifies the nature of the data which must be submitted. Section 505(d), 21 U.S.C. § 355(d), enumerates the grounds upon which the Secretary shall disapprove such application, while Section 505(c), 21 U.S.C. § 355(c), commands that if none of such grounds exist he shall approve the application. Section 505(d), 21 U.S.C. § 355(d), requires that the applicant be given an opportunity for a hearing and *authorizes the Secretary to determine* whether the data submitted includes adequate tests to establish the drug's safety, whether the results of such tests show that the drug is safe, whether the proposed methods of manufacture are adequate, whether the drug will have the effect it purports or is represented to have, and whether the labeling proposed is false or misleading in any particular. Similarly, Section 505(e), 21 U.S.C. § 355(e), authorizes the Secretary to make such determinations after notice and opportunity for hearing if he proposes to withdraw approval of an application previously granted. Section 505(h), 21 U.S.C. § 355(h), authorizes the applicant to appeal to a United States Court of Appeals from orders of the Secretary refusing or withdrawing approval of an application, and provides that the finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive.

Thus, "the agency does have direct authority to enforce [a] regulation in the context of passing upon applications for clearance of new drugs, § 505, 21 U.S.C. § 355 . . . ." *Abbott Laboratories, et al.* v. *Gardner,* 387 U.S. 136, 152 (1967). However, no provision of the Act gives the FDA comparable direct regulatory authority to make a binding determination as to whether a drug is "generally recognized as safe and effective."

II. The Five Cases Before The Court

There is a basic factual distinction which must be kept in mind in considering the five cases before the Court. The drugs involved in *Bentex* and two of the drugs involved in *USV* have never been the subject of an NDA. In contrast, the drugs involved in *Hynson* and *CIBA* and the remaining drugs involved in *USV* had all been the subject of effective NDA's prior to marketing.

A. The Bentex Case

The drugs involved in *Bentex* were marketed by their manufacturers prior to 1962 without filing an NDA, on the grounds that at the time of their introduction they were generally recognized as safe. After receipt in 1970 of an advisory letter from the FDA that their drugs were "new drugs" which were not marketable because no NDA had been filed, the manufacturers brought a declaratory judgment action in the District Court. The District Court referred to the FDA for administrative determination, after notice and hearing, the question whether the drugs involved were "new drugs." This case therefore poses directly the question whether the Food and Drug Administration has statutory authority to make a legally binding administrative determination as to whether drugs which had never been the subject of an NDA were "new drugs" as defined in the Act.[4] The Court of Appeals reversed and remanded the case to the District

[4] The same question is not directly before the Court with respect to the non-NDA'ed drugs involved in *USV*. There the District Court in a declaratory judgment action determined after trial that the non-NDA'ed drugs were not "new drugs" because exempted under the provisions of the "grandfather" clause in the 1962 Amendments. § 107(c)(4) of P.L. 87-781. The Government has abandoned its challenge to the District Court's exercise of jurisdiction to hear and decide this case on the merits.

Court for determination of this question, holding, we believe properly, that the FDA does not have authority to decide in an administrative proceeding whether a drug for which no NDA has been filed is a "new drug."

The Government's brief as petitioner in *Bentex* discusses a subsidiary issue as to whether withdrawal of approval of an NDA covering one drug represents a binding administrative determination of a different manufacturer's right to continue to market a similar drug which has never been the subject of an NDA. However, the Court of Appeals did not treat this issue in its opinion in *Bentex,* observing in a footnote that the Government's argument had been described by a commentator as "lacking in merit," and in any event involved disputed issues of fact which "may be inquired into on remand." 463 F.2d at 368, fn. 18; Joint App. 264. The issue is treated more extensively in the same court's opinion in *USV,* discussed *infra,* pp. 14-15.

B. The CIBA Case

The drug involved in *CIBA* had been the subject of an NDA which became effective before 1962 based upon proof of safety. In 1969, as the result of a report received from a panel of the National Academy of Sciences-National Research Council, the FDA indicated its intention to withdraw approval of the NDA. Following promulgation of revised regulations governing such withdrawal proceedings, the FDA in 1970 issued a formal notice of its intention to withdraw approval. The manufacturer requested a hearing, and advised the FDA that it contended that its drug was not a "new drug" and that its request for a hearing was "made with a reservation of the right to establish these facts in the administrative proceedings, or in

judicial proceedings, or both." The FDA denied the request for a hearing and issued an order withdrawing approval of the NDA. On appeal the Court of Appeals affirmed the order.

Prior to the FDA's final order withdrawing approval of the NDA, the manufacturer filed an action for a declaratory judgment to determine whether its drug was a "new drug." After issuance of the FDA's final order but before the appeal was heard, the District Court dismissed the action on the ground that even if it had jurisdiction it would exercise its discretion and refuse to determine the question presented. On appeal the Court of Appeals affirmed this dismissal on the grounds that the FDA has primary jurisdiction to adjudicate whether a drug is a "new drug" and had necessarily decided that question in the administrative proceeding withdrawing approval of the NDA; and that the question was subject to review on direct appeal. The case thus presents a related but different question from that posed in *Bentex:* Whether the FDA's statutory authority to withdraw its prior approval of an NDA depends upon a prior determination that the subject drug is still a "new drug" as defined in the Act. We submit that the FDA does not have authority to adjudicate whether a drug is a "new drug," that this question is not presented in a proceeding to withdraw the FDA's prior approval of a New Drug Application, that the action of the District Court was an abuse of its discretion, and that the holding of the Court of Appeals was erroneous.

C. The Hynson Cases

In *Hynson* the procedural history is somewhat different, but the cross-petition in No. 72-414 presents the same basic question as does the petition in *CIBA.*

Again, the drug involved was marketed before 1962 after an NDA became effective on the basis of proof of safety. Again, based on the report of an NAS-NRC review panel, and after giving the manufacturer an opportunity to submit additional data, the FDA published a formal notice of its intention to withdraw approval of the NDA. The manufacturer requested a hearing, reserving the right to contest the jurisdiction of the FDA in the administrative proceedings, or in judicial proceedings, or in both, based on the contention that the drugs were no longer "new drugs" as defined in the Act.

Before any action had been taken on this request, the manufacturer filed an action for a declaratory judgment, asking for a determination as to whether its drug was a "new drug," and alleging as one of its grounds that "the contemplated administrative hearing will not offer an opportunity to plaintiff to contest the jurisdiction of defendants on the ground that [the drugs] are not 'new drugs'." Joint App. 17. The District Court dismissed the suit on the ground that these issues were within the primary jurisdiction of the FDA and that the manufacturer had failed to exhaust its administrative remedies. The court directed "an agency determination on the record made before the agency" of the issues as to whether the drugs were generally recognized as safe and effective or exempted from the effectiveness provisions of the Act by the 1962 "grandfather" clause. Joint App. 23.

No appeal was taken from this order of dismissal. Instead the manufacturer requested a hearing by the FDA on these questions. The FDA denied the request for a hearing and issued an order withdrawing approval of the NDA. On direct appeal from the

Commissioner's order, the Court of Appeals reversed the FDA's order because of its refusal to grant a hearing.

However, that court held that a hearing was required on the issue of whether the agency's approval of the NDA should be withdrawn, not as to whether the drug involved was still a "new drug." The Government, as petitioner in No. 72-394, asserts error in requiring a hearing on the issue of withdrawal; and the manufacturer, as the cross-petitioner in No. 72-414, apparently asserts error in the failure to require a hearing on two additional issues: (1) whether the drug is exempted from administrative withdrawal of approval of its NDA by Section 107(c) of the 1962 Amendments; and (2) whether the drug is still a "new drug." We express no opinion as to whether the manufacturer was entitled to a hearing on the issue of withdrawal, but submit that the court properly limited its remand to that issue, because no drug is exempted from a proceeding to withdraw approval of its NDA by Section 107(c), and the question of new-drug status is not presented in an administrative proceeding to withdraw approval of an NDA.

D. The USV Case

As indicated above, the *USV* case involves both drugs which were the subjects of pre-1962 NDA's, which "became effective" based on proof of their safety, and similar drugs which the same manufacturer marketed without filing an NDA based on the general recognition of their safety. The case does not present the issue as to the FDA's authority to adjudicate new-drug status, because the Government does not challenge here the jurisdiction of the District Court in a declara-

tory judgment action to decide that question. The District Court held both the NDA'ed and non-NDA'ed drugs to be exempt from the "effectiveness" provisions of the Act by the 1962 "grandfather" clause. The Court of Appeals reversed, holding *first,* that Section 107(c)(4) of the 1962 Amendments does not apply to a drug marketed after an NDA is approved (or becomes effective); and *second,* we think incorrectly, that if an NDA covering one drug is effective, another similar drug marketed *by the same manufacturer* without an NDA was nevertheless "covered by an effective application"—i.e., that of the "pioneer" drug—and thus not exempt under Section 107(c)(4) of the 1962 Amendments.

The Government now confesses that this distinction, based on whether the "me-too" drug was marketed by the same or a different manufacturer, is erroneous, but argues that the court was correct in reversing. The Government contends that withdrawal of an approved NDA covering one drug represents a binding administrative determination of the right of *any* manufacturer to market a similar drug which has never been the subject of an NDA. We disagree.

ARGUMENT

I. Introduction and Summary

The Government's lead brief in these consolidated cases is its Brief for Petitioner in No. 72-555, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.* In it the Government seeks nothing less from this Court than a sweeping grant of authority to make a binding legal determination in administrative proceedings of its own contriving as to whether every drug now on the market can continue to be marketed and for what

purposes. It asks this Court totally to ignore the provisions of the governing statute and the administrative interpretation and judicial construction of that statute extending over a period of thirty-five years. It asks the Court to grant it authority to adjudicate factual issues which Congress has committed to the courts, and to issue regulations having the force of law as to matters in which no legislative authority has been delegated.

On the other hand, some of the drug manufacturers involved in these cases seek to have the Court impose limitations on the the authority of the Food and Drug Administration beyond those imposed by the literal terms of the statute or intended to be imposed by the Congress.

Both the Government and some of the manufacturers urge upon the Court strained constructions of the transitional provisions, the "grandfather" clause, contained in the Drug Amendments of 1962. A number of the questions presented in these cases are resolved by giving effect to the literal terms of and Congressional intent with respect to these provisions.

The provisions of the Act which must govern these cases, while sometimes convoluted, are essentially clear. In the basic Act passed in 1938 Congress sought to insure that before new drugs were introduced an expert scientific agency should be satisfied as to their safety. Congress considered that a "new drug" was one which had not been on the market for a substantial length of time so as to become generally recognized as safe. They exempted from pre-marketing clearance by the agency drugs already on the market, but provided that all drugs, old or new, could be removed from

the market by seizure and condemnation, or their distribution enjoined, if they were adulterated or unsafe for use as directed or if their labeling were false and misleading.

The amendments enacted in 1962 did not change this basic approach. New drugs henceforth would be required to show by acceptable scientific evidence that they were both safe and effective before they could be marketed. Manufacturers of drugs already cleared for safety by the agency under an NDA were not required to submit new applications demonstrating their effectiveness, except for new claims made after 1962, unless the agency withdrew its prior approval for lack of effectiveness, and this the agency was not authorized to do for two years from the date of enactment. Drugs already on the market without an approved NDA, on the basis that they were generally recognized as safe, were permanently exempted from becoming "new drugs" by reason of the changed definition which in the future would require general recognition of both safety and effectiveness to avoid the new drug procedures, but only on the condition that no new claims are made for the drug.

The Act does not contemplate or authorize the FDA to make a binding determination in an administrative proceeding as to whether a drug for which no New Drug Application has been filed is a "new drug," or is adulterated, or is misbranded. The agency may investigate suspected violations (§ 702, 21 U.S.C. § 372), but it is the District Courts of the United States which have jurisdiction to restrain violations (§ 302, 21 U.S.C. § 332), and it is in the District Courts of the United States that a drug in violation of the Act may be "proceeded against . . . and condemned" (§ 304, 21 U.S.C. § 334).

Factual determinations which the agency is not authorized to make in an adjudicatory proceeding with respect to a particular drug it is likewise not authorized to make in a rule-making proceeding which purports to apply to all drugs or to all drugs of a particular type. Similarly, what the FDA cannot adjudicate directly it likewise cannot adjudicate indirectly. The Act neither contemplates nor authorizes that an order of the agency withdrawing approval of a New Drug Application should have binding legal effect upon the right to market other drugs never the subjects of New Drug Applications, because of their similarity to the drug subject to the order.

On the other hand, the FDA is not only authorized but also mandated by the statute to withdraw its approval of a New Drug Application whenever, on the basis of later information, it makes the requisite statutory findings as to the drug's lack of safety or effectiveness. The two-year moratorium on the FDA's authority to withdraw approval of an NDA for lack of effectiveness, provided by Section 107(c)(3) of the 1962 Amendments, has expired; and in none of the cases before the Court did the agency attempt such withdrawal before that moratorium ended. The "grandfather" provision contained in Section 107(c)(4) of the 1962 Amendments does not exempt *any* drug from an administrative proceeding to withdraw approval of its New Drug Application, because Section 107(c)(4) does not apply to a drug which has been the subject of a New Drug Application.

Several of the parties involved in these cases contend that a drug which was once a "new drug," and was originally marketed pursuant to a New Drug Application, may subsequently become "generally recognized

as safe and effective" and thus cease to be a "new drug." They explicitly urge, or assume, that the right to market such drug no longer depends upon an approved New Drug Application. This construction has been adopted by officials of the agency in the past and appears to be accepted by the Government.

However, even if one accepts the premise that the manufacturer of a drug marketed pursuant to an approved New Drug Application can continue to market that drug after approval is withdrawn, if the drug has become generally recognized as safe and effective, it does not follow that such general recognition terminates the right of the agency to withdraw its prior approval of the NDA.

To retain approval of its NDA, a drug must meet the specific standards of the statute, and a strong case can be made that the medical and scientific community is entitled to know whether it meets such standards. Not only is there nothing in the statute to suggest that the agency's right to withdraw its approval is terminated if a drug becomes generally recognized as safe and effective, but also the statute on its face mandates such withdrawal if the statutory standards for continued approval are not met. The fact that the Congress enacted a specific provision suspending such right of withdrawal on grounds of effectiveness suggests that had it intended to impose further limitations on the agency's withdrawal of approval it would have done so.

Since the agency's right and duty to withdraw approval under certain circumstances are not affected by a drug's achieving general recognition, whether the drug has achieved such recognition is not an issue in the administrative proceeding to withdraw approval of the NDA. Moreover, to hold otherwise would mark the

virtual end of the agency's summary judgment procedure, because it would require as a practical matter that a hearing be held in almost every administrative proceeding to withdraw approval. Since the determination as to whether a drug is generally recognized as safe and effective involves adjudicative facts, a hearing would be required by due process whenever a genuine issue was raised as to such recognition.

In the cases before the Court, the lower courts have not dealt with the question of whether a drug, the NDA for which has been withdrawn, can remain on the market on the basis of general recognition of its safety and effectiveness. However, upon remand of *CIBA*, this issue would be directly posed in the declaratory judgment action to determine the plaintiff's right to continue to market the drug on such basis.

If this Court should affirm the foregoing view as to the system of administrative and judicial enforcement established by the Act, none of the dire predictions made by the Government would come to pass. It is highly unlikely that the widespread litigation which the Government fears will ever occur, particularly if the Court rejects the strained constructions of the "grandfather" provisions which are urged upon it.

In such litigation as does occur, the District Courts are perfectly well able to determine whether a drug is "generally recognized as safe" or "generally recognized as safe and effective," as they have been doing effectively since passage of the Act in 1938. This is a simple inquiry into the nature of expert opinion about the drug, and requires no technical or scientific expertise of the kind involved in the agency's approval of a New Drug Application.

What the Government in fact desires, the determination by the agency of all factual questions with respect to all drugs without hearings, would require sweeping changes in the Constitution as well as in the basic statute.

II. The Food and Drug Administration Has No Authority To Make a Legally Binding Administrative Determination as to Whether a Drug Which Has Never Been the Subject of a New Drug Application Is a "New Drug"

A. The FDA Has No Authority To Adjudicate This Issue

Unless an NDA has been filed, the FDA's statutory role is prosecutorial, not adjudicatory. The Commissioner has no authority under the Act, either through adjudication or rule-making, to make a conclusive factual finding as to whether a drug which has never been the subject of a New Drug Application is a "new drug." This is a question for the courts.

The Act clearly contemplates and authorizes administrative enforcement of its provisions with respect to a New Drug Application. The Commissioner's authority with respect to an NDA is comprehensive and unequivocal. The House Committee's report on the 1938 Act shows that Congress clearly intended to grant such authority. It speaks of "*authoritative* review of the manufacturer's tests" and of "decisions of the administrative agency" which are subject to court review.[5] However, he has no such authority to deal administratively with drugs which have been marketed without the manufacturer's filing of a New Drug Application—whether it claims exemption from his regulatory regime because of their general acceptance as

[5] H.R. Rep. No. 2139, 75th Cong., 3d Sess. 9 (1938).

safe and effective drugs or because they are within the exemptive "grandfather" provision. Thus, if a drug subject to an NDA is "misbranded," the Commissioner has authority to proceed against it administratively by withdrawing approval. However, if a drug which he has not approved is misbranded, his sole means of enforcing the Act's prohibitions against the drug is by bringing a civil or criminal action authorized by the statute.

As the Court of Appeals recognized in its opinion in *Bentex,* the FDA's role with respect to a non-NDA'ed drug is that of prosecutor, not judge or lawmaker:

> "The FDA has neither primary jurisdiction, as the defendants argue, nor concurrent jurisdiction, as the District Court concluded, to adjudicate whether a product is an old or a new drug. It may, in its prosecutorial role, reach a conclusion that a product being marketed is a 'new drug' requiring pre-marketing approval; but that opinion is not adjudicatory, it is only the basis on which the FDA, as the prosecutor or initiator of either a seizure or injunctive action in the District Court, may invoke the jurisdiction of that Court to determine, among other issues, whether the drug challenged is a 'new drug'. There is manifestly no provision in the Act for an administrative proceeding before the Secretary to compel the filing of a 'new drug' application or to halt the marketing of a drug for which there is no approval by the Secretary. It is not without significance that, so far as the official reports reflect, the Secretary has never attempted directly to exercise such jurisdiction. * * * The only adjudicatory right vested by the Act in the Secretary relates to approval, or withdrawal of an approval, of a 'new drug' application." *Bentex Pharmaceuticals, Inc., et al.* v. *Richardson,* 463 F.2d 363, 370, 371 (4th Cir. 1972); Joint App. 266, 267.

In fact, the FDA's role as a prosecutor was recognized by this Court in its opinion in *Ewing* v. *Mytinger & Casselberry, Inc.*, 339 U.S. 594 (1950). There the Court considered whether a decision to institute such a civil action could be enjoined. Section 304(a) of the Act (21 U.S.C. § 334(a)) authorizes *multiple* seizures of misbranded articles "when the Secretary has probable cause to believe from facts found, without hearing, ... that the misbranded article is dangerous to health, or that the labeling of the misbranded article is fraudulent, or would be in a material respect misleading to the injury or damage of the purchaser or consumer." Such multiple seizures were ordered through libel actions, and the manufacturer of the drug involved brought an action seeking to challenge directly the finding of probable cause. In its opinion in *Abbott Laboratories, et al.* v. *Gardner*, 387 U.S. 136 (1967), the Court described its prior holding as follows:

> "This Court held that the owner could raise his constitutional, statutory, and factual claims in the libel actions themselves, and that the mere finding of probable cause by the Administrator could not be challenged in a separate action. That decision was quite clearly correct. . . . The Court in *Ewing* first noted that the 'administrative finding of probable cause required by § 304(a) is merely the statutory prerequisite to the bringing of the lawsuit,' at which the issues are aired. 339 U.S., at 598. * * * Second, the determination of probable cause in *Ewing* has 'no effect in and of itself,' 339 U.S., at 598; only some action consequent upon such a finding could give it legal life." 387 U.S. at 147.

Similarly, if the FDA determines that a New Drug Application should have been filed covering a marketed drug, because it believes that the drug is not generally

recognized as safe and effective, or the FDA determines that a drug's labeling is false and misleading, this "has 'no effect in and of itself' . . . ; only some action consequent upon such a finding could give it legal life"—*i.e.*, "the bringing of a law suit."

This has been the unchallenged view of the statute since its enactment in 1938. Whether a particular drug was generally recognized as safe and effective has been regarded as a question of fact to be determined by the court in an action to seize the drug or enjoin its distribution. *United States* v. *One Device*, * * *, 160 F.2d 194 (10th Cir. 1947); *AMP Incorporated* v. *Gardner*, 389 F.2d 825 (2d Cir. 1968); *United States* v. *Articles of Drug* * * * *"Quick-O-Ver,"* 274 F.Supp. 443 (D. Md. 1967); *United States* v. *7 Cartons* * * *"Ferro-Lac* * * *," 293 F.Supp. 660 (S.D.Ill. 1968). Similarly, whether the labeling of a drug was false or misleading has been held to be a question of fact to be determined by the court in a civil or criminal action. *United States* v. *Kordel*, 164 F.2d 913 (7th Cir. 1948), *aff'd*, 335 U.S. 345 (1948); *Woodward Laboratories, Inc.* v. *United States*, 198 F.2d 995 (9th Cir. 1952); *United States* v. *Schlicksup Drug Co.*, 206 F.Supp. 801 (S.D.Ill. 1962); see also *Van Liew* v. *United States*, 321 F.2d 664 (5th Cir. 1963).

When the *Bentex* case was before the District Court, the Government, in total defiance of the Act and all judicial precedent, contended that the FDA has "primary and exclusive jurisdiction" to determine whether a drug is a "new drug," even when, as in *Bentex*, the drug had never been the subject of a New Drug Application. The District Court rejected this argument, and the Government did not assert its "primary and ex-

clusive jurisdiction" on appeal. While acknowledging that, because of its failure to appeal, this issue "is not presented in this Court," the Government nevertheless warns: "The agency believes, however, that it has primary jurisdiction over 'new drug' status, safety and effectiveness, and it will continue to assert this position where appropriate." Brief for Petitioners, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.*, No. 72-555, pp. 46-47, fn. 76.

It appears that the Solicitor General does not agree with the claim of "the agency" that it has "primary and exclusive jurisdiction." The Government states in another footnote: "Of course, we do not deny that in enforcement proceedings the district court must decide whether a product is a 'new drug' subject to regulation, at least where the issue has not been litigated before the agency. See, *e.g., Bentex Ulcerine, supra.*[6] But the existence of such power in the courts is not inconsistent with its existence in the agency." *Id.* at p. 57, fn. 82. Even this concedes too little to the District Courts, in two respects. *First,* the expression of the FDA's opinion that the Act is being violated permits the manufacturer to bring an action for a declaratory judgment. *AMP, Inc.* v. *Gardner,* 389 F.2d 825, 826, and n. 2 (2d Cir. 1968), *cert. denied,* 393 U.S. 825 (1969). *Second,* the FDA has no authority to make a legally binding determination, the issue has never "been litigated before the agency," and the court is not ousted of jurisdiction by prior expression of opinion by the FDA.

The District Court, while holding that it had jurisdiction to determine new-drug status in an action for

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[6] *United States* v. *An Article of Drug, "Bentex Ulcerine,"* 469 F.2d 875 (5th Cir. 1972).

a declaratory judgment and thus rejecting the argument that the FDA had "primary and exclusive jurisdiction," concluded that the FDA had "concurrent jurisdiction" and promptly referred the issue to the agency for determination. The Court of Appeals properly held that, "The FDA has neither primary jurisdiction, as the defendants argue, nor concurrent jurisdiction, as the District Court concluded, to adjudicate whether a product is an old or a new drug." *Supra*, p. 22.

The District Court reasoned that the statutory "grant of authority to approve or withhold approval of [a] new drug application, or to proceed with regulatory action in the courts, necessarily implies authority for F.D.A. to determine the threshold question of whether the article involved is a drug which requires an approved new drug application for lawful interstate shipment." Joint App. 255. Similarly, the Government argues that reference to the administrative agency is appropriate "where the question of an agency's threshold jurisdiction turns on the resolution of technical questions of fact of a kind arguably within the competence of the agency"; and that, "in conferring on the agency comprehensive powers to perform its mission, [the Congress] necessarily included the threshold power to decide whether products are 'new drugs' over which it has jurisdiction." *Id.* at pp. 59, 60.

What all of this conveniently overlooks is the factual situation in the case which was before the court. The FDA's claim of authority, never explicitly granted and never before asserted, to determine the "threshold question" of its jurisdiction, could arise only where that jurisdiction has been invoked by the filing of an NDA, since "[t]he only adjudicatory right vested by

the Act in the Secretary relates to approval, or withdrawal of an approval, of a 'new drug' application." *Bentex Pharmaceuticals, Inc.* v. *Richardson,* 463 F.2d 363, 371 (4th Cir. 1972); Joint App. 267. No NDA had been filed covering the drugs involved in *Bentex,* no manufacturer had asked the FDA to decide anything, and it was the agency which asserted *sua sponte* that the continued marketing of the drugs without NDA approval was a violation of the Act. As is discussed *infra,* pp. 65-73, even in a proceeding to withdraw approval of an NDA there is no "threshold question" of the agency's "jurisdiction"; but clearly no question of "jurisdiction" is presented when there is no proceeding or application before the agency.

The District Court's suggestion that such a "threshold question" is presented for agency determination because of the agency's authority "to proceed with regulatory action in the courts" totally misconceives the agency's role. Nothing in the Act or in the agency's regulations contemplates that the FDA make an administrative determination of an adjudicative fact as a prerequisite to its instituting civil or criminal enforcement actions in the courts. As this Court held in *Ewing* v. *Mytinger & Casselberry, supra,* even a statutory finding that there is probable cause to believe that the Act has been violated, and that public injury will result, is not an adjudication, but only a more formalized decision of the prosecutor. Absent such formal finding, it is even clearer that if the FDA concludes that a product is being illegally marketed because it is a "new drug" and no NDA has been filed, "that opinion is not adjudicatory, it is only the basis on which the FDA, as the prosecutor or initiator of either a seizure or injunction action in the district court, may invoke

the jurisdiction of that Court to determine . . . whether the drug challenged is a 'new drug'." *Id.* at p. 370; Joint App. 266.

In fact, the referral to the agency by the District Court returned to the prosecutor the task of judging the validity of charges already filed by him. As early as August 1969 the FDA had published its opinion as to the answer to the question returned to it for resolution, stating that its contemplated order "will cause any such drug on the market to be a new drug for which an approved new-drug application is not in effect . . . ." 34 Fed. Reg. 13674; Joint App. 227. The FDA had already advised Bentex Pharmaceuticals, Inc., that its drugs were new drugs and no longer marketable. Joint App. 254, n. 3. The agency's prosecutorial role, and the fact that it had already reached and publicly declared its opinion, also argues that the District Court was incorrect in concluding that the FDA was "the more able arbiter of the question." Joint App. 256.

The Government acknowledges that *CIBA*, the only case holding that it has authority to make an administrative determination as to whether a drug is a "new drug," "arose in the context of a proceeding for withdrawal or approval of an NDA." Brief for Petitioners, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.*, No. 72-555, p. 49. However, the Government views this distinction as a procedural detail of no significance:

> "But even where the manufacturer has no NDA in effect or is not seeking approval for one, so that the determination of the 'new drug' question would not be ancillary to any proceeding specifically prescribed by the Act, a procedure is available where-

> by the agency may determine the issue. The Administrative Procedure Act expressly enables FDA, like any other administrative agency, to issue 'a declaratory order to terminate a controversy or remove uncertainty' (5 U.S.C. 554(e)). The present case [*Bentex*] illustrates an appropriate occasion for the exercise of the agency's declaratory order authority . . . ." *Id.* at pp. 49-50.

Of course, the fact that the agency could devise a procedure to conduct an adjudication would not remedy its lack of statutory authority to decide the question involved. However, in this instance, even the procedure it cites is not available to it.

Former Section 5(d) of the Administrative Procedure Act, now 5 U.S.C. § 554(e), which provides that "[t]he agency, with like effect as in the case of other orders, and in its sound discretion, may issue a declaratory order to terminate a controversy or remove uncertainty," authorizes an agency to decide by declaratory order only questions which it is authorized to decide in the first place. *Boston & M.R.R.* v. *United States,* 162 F. Supp. 289, 293-294 (D. Mass. 1948), *appeal dismissed,* 358 U.S. 68 (1958). Moreover, 5 U.S.C. § 554 applies by its terms only in the "case of adjudication required by statute to be determined on the record after opportunity for an agency hearing." This has never been in doubt. The following discussion appears in the *Attorney General's Manual on the Administrative Procedure Act,* 1947, p. 59:

> "This grant of authority to the agencies to issue declaratory orders is limited by the introductory clause of section 5 so that such declaratory orders are authorized only with respect to matters which are required by statute to be determined 'on the record after opportunity for an agency hearing'.

> In addition, if the subject matter falls within one of the numbered exceptions in the introductory clause of section 5, such as a matter in which an agency is acting as an agent for a court, section 5(d) does not apply. Sen. Rep. p. 18; H.R. Rep. p. 31 (Sen. Doc. pp. 204, 263) For example, where an agency is authorized after hearing to issue orders to cease and desist from specified illegal conduct, it may, under section 5(d), if it otherwise has jurisdiction, issue a declaratory order declaring whether or not specified facts constitute illegal conduct. On the other hand, while the Securities and Exchange Commission has long issued informal advisory interpretations through its principal officers as to whether a proposed issue of securities would be exempt from the registration requirements of the Securities Act, there is no statutory agency hearing procedure in which this question can be determined; if securities are sold without registration and the Commission believes that registration was required, it can only institute civil or criminal proceedings. Accordingly, section 5(d) does not authorize the Commission to issue declaratory orders as to whether particular securities must be registered under the Securities Act."

Both of the cases cited by the Government as analogous to its proposed use of a declaratory order (*Frozen Food Express* v. *United States,* 351 U.S. 40 (1956), and *Red Lion Broadcasting Co.* v. *Federal Communications Commission,* 395 U.S. 367 (1969)) involved orders relating to a matter that the agency had unquestioned authority to adjudicate. The Government's own statement of the holding in *Red Lion Broadcasting* reveals the basic limitation on the declaratory procedure: "... since FCC could have conducted adjudicatory proceedings ... 'it could, under the Administrative Procedure Act, have issued a declaratory order ....'"

Brief for Petitioners, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.*, No. 72-555, p. 50.

Nothing better illustrates how tenuous is the Government's position than does its reliance on Section 5(d) (5 U.S.C. § 554(e)) to reinforce its claim that it has authority to make an administrative determination of new-drug status. This is not a determination which the FDA is authorized by statute to make, much less one "required by statute to be determined on the record after opportunity for an agency hearing." Thus the declaratory-order provision of the Administrative Procedure Act is not available to it for this purpose.[7]

The only procedural alternative to a declaratory order cited by the Government is that it might resort to "rule-making under Section 701(a) . . . to classify categories of drugs as generally recognized as safe and effective, rather than dealing with each drug separately." *Id.* at pp. 50-51. However, resort to this procedure is also denied to the agency under the statute.

B. The FDA Has No Authority To Decide This Issue by Rule-Making

One of the Government's principal arguments for reversal of the decision of the Court of Appeals in *Bentex* is totally unrelated to the question of whether

[7] Even if the declaratory procedure were to be used with respect to an NDA'ed drug, as an alternative to a proceeding to withdraw approval of the NDA under Section 505(e) of the Act, arguably it would not be available, because the determination involved would be within the exception made by Section 554(a)(1), as "a matter subject to a subsequent trial of the law and facts *de novo* in a court" in a seizure or injunction action. Were the question referred to the agency for initial determination by a court in which an action for a declaratory judgment was pending, the declaratory procedure would seem to be barred by the exception in Section 554(a)(5), as a case "in which the agency is acting as an agent for a court."

that court was correct in concluding that the FDA has no authority to determine in an administrative proceeding whether a drug which has never been the subject of a New Drug Application is a "new drug" as defined in the Act, and thus is being marketed illegally. In its brief in *Bentex,* the Government complains that the decision below would undermine its attempt to determine the same factual question through rule-making.

The Government asserts: "Denial of the power to pass upon questions of 'new drug' status * * * would seriously undermine FDA's program of reviewing the status of and establishing standards for over-the-counter drugs." Brief for Petitioners, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.,* No. 72-555, p. 58. This program it describes as "a procedure for determining in substantive rule making, by therapeutic class, whether particular OTC products not covered by NDA's are generally recognized as safe and effective and not misbranded, under the standards of the Act" (*Id.* at p. 24), which would result in the issuance of regulations "which could thereafter be enforced in the courts as binding" (*Id.* at p. 25).

The Government's argument is thus stated in the "Introduction and Summary":

> "Moreover, the implications of the decision below extend beyond the area of prescription drugs involved in the present case. The agency's current program to review the over-the-counter drugs . . . would also be undermined by the court of appeals' rationale, since the agency would have no power to determine definitively, subject to judicial review, standards by which hundreds of thousands of drugs for which no NDA is in effect may

be classified as 'new drugs' or not. The agency would be required to pursue these products throughout the courts of the Nation in innumerable trials considering *de novo* issues that are best suited to administrative resolution and that may, indeed, already have been given careful consideration in administrative proceedings." *Id.* at pp. 36-37.

In contrast to this bleak prospect, the Government suggests that, if this Court holds that the agency has authority to determine new-drug status definitively, "FDA may, as in the case of over-the-counter drugs . . . , promulgate procedures for rule-making under Section 701(a) (21 U.S.C. 371(a)) to classify categories of [prescription] drugs as generally recognized as safe and effective, rather than dealing with each drug separately." *Id.* at pp. 50-51.

The Government's reference to its OTC review procedure to justify reversal of *Bentex* places both *amicus* and the Court in a difficult position. The issue of the agency's authority to make a binding determination as to a drug's new-drug status in a rule-making proceeding is not before the Court. The Government seeks premature validation of this rule-making procedure although it is fully aware that the agency's authority to make such determination through rule-making has been seriously challenged, and that the issue may ultimately have to be resolved by this Court.

In view of the Government's attempt to use the OTC regulations to support its argument in *Bentex, amicus* feels it has no alternative but to deal with the agency's lack of rule-making authority more fully than would otherwise be appropriate in these cases. It does so, not in an effort to induce the Court to decide an issue

which is not before it, but to seek to persuade the Court that neither the OTC review nor the prospect of the agency's resort to rule-making with respect to non-NDA'ed prescription drugs offers any reason to adopt the Government's position in *Bentex*.

The Government is correct in concluding that factual questions which the FDA is not authorized to decide, but which must be decided by the courts, cannot be decided by the FDA through rule-making. Moreover, not only does the agency lack adjudicatory authority, it is not authorized by the Act to issue substantive or legislative regulations, having the force of law, specifying which of the non-NDA'ed drugs on the market are generally recognized as safe and effective and not misbranded. It is hardly tenable to suggest that the Court should approve one unauthorized action to avoid undermining a second unauthorized action.

The procedure for the FDA's review of OTC drugs was published on May 11, 1972. 37 Fed. Reg. 9464 *et seq.* It is briefly described in the Government's Brief for Petitioners, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.*, No. 72-555, at pp. 24-25. The general procedure established by these regulations is that OTC drugs will be classified into twenty-six broad, therapeutic categories. An advisory review panel will be appointed to review each category and will prepare proposed monographs defining conditions under which drugs in each category will be generally recognized as safe and effective and not misbranded. The industry will be invited to submit data to the panels, but the regulations specify standards of proof which the panels will apply. After review of the recommendations of the panels, the Commissioner will publish a tentative order

containing a proposed monograph to which objections may be filed. Thereafter he will publish a final monograph "establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded." These regulations are described in greater detail in the Appendix.

It is of course perfectly appropriate for the Commissioner to undertake a general review of OTC drugs now on the market, to secure the advice of panels of experts who have special training and experience in the use of particular categories of such drugs, and to afford interested parties an opportunity to present data and recommendations to those panels. Moreover, it is both appropriate and desirable for the Commissioner, after review of the recommendations of the panels, to set out in a public notice his opinion as to which formulations are and are not generally recognized as safe and effective, and as to which labeling claims are permissible. All this could be accomplished through publication of interpretive regulations, or guidelines, which would inform the industry as to the Commissioner's position and recommendations—the procedure generally and successfully used in the past.

The Proprietary Association believes that the extensive review which the FDA has undertaken could result in most of the problems which have been raised with respect to OTC drugs being resolved by agreement between the agency and the industry. The Proprietary Association has co-operated fully with the scientific panels which have been convened to date, and expects to continue to do so. However, from the first proposal of this procedure, both The Proprietary Association and the Pharmaceutical Manufacturers Asso-

ciation have objected that the agency has no authority to issue these monographs as binding regulations, having the force of law, and thereby oust the U.S. District Courts of jurisdiction to determine the factual questions which may be presented with respect to a particular drug which does not comply with the monograph.

In predicting that similar procedures may be adopted to classify categories of prescription drugs, which have never been the subject of an NDA, as generally recognized as safe and effective, the Government cites as its authority for proceeding in this way *Abbott Laboratories* v. *Gardner,* 387 U.S. 136, 147, 149-152 (1967), and *CIBA-Geigy Corporation* v. *Richardson,* 446 F.2d 466 (2d Cir. 1971). Brief for Petitioners, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.,* No. 72-555, p. 51. These same decisions were cited by the Commissioner in his comments preceding the final regulations establishing the OTC review.

The Commissioner there asserts: "In *Abbott Laboratories* v. *Gardner*, 387 U.S. 136, 151-152 (1967), the Supreme Court stated that regulations issued under 701(a) of the Act, if within the Commissioner's authority, 'have the status of law and violations of these carry heavy criminal and civil sanctions.'" 37 Fed. Reg. 9471. The quoted comment occurred in the course of the court's discussion as to whether the regulations there involved were ripe for review in an action for a declaratory judgment. The following extract is sufficient to recall the context of the Court's statement:

> "The Government argues, however, that the present case can be distinguished from cases like *Frozen Food Express* on the ground that in those instances the agency involved could implement its

policy directly, while here the Attorney General must authorize criminal and seizure actions for violations of the statute. In the context of this case, we do not find this argument persuasive. These regulations are not meant to advise the Attorney General, but purport to be directly authorized by the statute. Thus, if within the Commissioner's authority, they have the status of law and violations of them carry heavy criminal and civil sanctions. * * *

"This is also a case in which the impact of the regulations upon the petitioners is sufficiently direct and immediate as to render the issue appropriate for judicial review at this stage. These regulations purport to give an authoritative interpretation of a statutory provision that has a direct effect on the day-to-day business of all prescription drug companies; its promulgation puts petitioners in a dilemma that it was the very purpose of the Declaratory Judgment Act to ameliorate. As the District Court found on the basis of uncontested allegations, 'Either they must comply with the every time requirement and incur the costs of changing over their promotional material and labeling or they must follow their present course and risk prosecution.' 228 F.Supp. 855, 861." 387 U.S. at 151-52.

The Court's holding was obviously correct, but just as obviously did not determine the question of the agency's authority. The final monographs contemplated by these OTC regulations also "purport to be directly authorized by the statute," and "if within the Commissioner's authority, they have the status of law . . . ." The issue is whether they are what they purport to be, which depends upon whether they are within the Commissioner's authority.

The Commissioner also cites, in paragraph 85 of his comments (37 Fed. Reg. 9471-72), the following passage from the opinion in *CIBA-Geigy Corporation* v. *Richardson*, 446 F.2d 466 (1971):

> " . . . the Commissioner has the power to issue binding interpretative regulations, e.g., Abbott Laboratories v. Gardner, 387 U.S. 136, 87 S.Ct. 1507, 18 L.Ed.2d 681 (1967). Indeed the particularization of a statute by rule-making is not only acceptable in lieu of protracted piecemeal litigation, e.g., Thorpe v. Housing Authority, 393 U.S. 268, 89 S.Ct. 518, 21 L.Ed.2d 474 (1969); NLRB v. Wyman-Gordon Co., 394 U.S. 759, 89 S.Ct. 1426, 22 L.Ed.2d 709 (1969), but it is the preferred procedure, e.g., Elman, A Note on Administrative Adjudication, 74 Yale L.J. 652, 654-55 (1965); see generally, Shapiro, The Choice of Rule Making or Adjudication in the Development of Administrative Policy, 78 Harv. L. Rev. 921 (1965)." 446 F.2d at 468.

As will be apparent from the foregoing discussion, the Court did *not* hold in *Abbott* that "the Commissioner has the power to issue binding interpretative regulations," but only that the regulations there involved purported to be binding and to have the force of law.[8]

In those instances in which the Commissioner was intended to have legislative authority, the delegation

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[8] The other cases cited by the court in *CIBA-Geigy* are not particularly relevant to the principle being asserted. The acceptability of rule-making in lieu of adjudication was neither the subject of nor discussed in the opinion in *Thorpe* v. *Housing Authority of the City of Durham*, 393 U.S. 268 (1969). *NLRB* v. *Wyman-Gordon Co.*, 394 U.S. 759 (1969), involved an attempt by the NLRB to make rules of "general . . . applicability and future effect" in an adjudicatory proceeding, without complying with the procedural requirements for rule-making imposed by 5 U.S.C. § 553. The case is discussed *infra*, p. 57.

of such authority in the Act was clear and unequivocal, and the violation of such regulations was made a prohibited act by Section 301 (21 U.S.C. § 331).

Section 401 of the Act, for example, authorizes the promulgation of regulations that establish a standard of quality for food. Sections 403(g) and (h) state that food which purports to be of a quality prescribed by regulations under Section 401 and which fails to comply with those standards is deemed misbranded and in violation of Section 301. A further example is found in Section 503(b)(3) which specifically provides that a prescription drug is deemed misbranded and in violation of the Act if it fails to include on the label various types of information required by regulations promulgated in accordance with Section 701(e).

Moreover, the legislative history of the Food, Drug, and Cosmetic Act emphasizes that in those instances in which Congress authorized the Commissioner to issue regulations having the force of law, it uniformly required that he afford affected parties an opportunity for an evidentiary hearing, and provided for judicial review on the record of such hearing. Thus, the House Committee Report on the 1938 Act states:

> "Section 701 relates generally to regulations. In the case of regulations, the violation of which constitutes an offense, it is required that appropriate notice of a public hearing be given and that adequate time shall be given after the promulgation of a regulation before it becomes effective." H.R. Rep. No. 2139, 75th Cong., 3d Sess. 9 (1938).

The statutory requirement for hearing is set out in Section 701(e) of the Act (21 U.S.C. § 371(e)). It provides that any regulation issued under certain specified sections of the Act be first published for comment, then

as a tentative order; that any person who will be adversely affected by such order may file objections thereto within thirty days and request a public hearing upon such objections; that the filing of such objections shall operate to stay the effectiveness of those parts of the order to which objections are made; that a public hearing must be held on the objections; and that the final order "shall be based on substantial evidence of record at such hearing and shall set forth, as part of the order, detailed findings of fact on which the order is based." Section 701(f) (21 U.S.C. § 371(f)) provides for judicial review of any final order issued under subsection (e) by the appropriate Court of Appeals, and provides that agency findings as to facts, if supported by substantial evidence, shall be conclusive.

The House Report thus described the applicability of these procedures:

> *"Procedure Governing Formulation and Judicial Review of Regulations*
>
> "Section 701(e), (f), and (g) of the committee amendment set forth the procedure governing the formulation and judicial review of certain regulations to be issued by the Secretary. These regulations include those with respect to the following matters: Establishing definitions and standards of identity, standards of quality, and standards of fill of container for foods (sec. 401); information on label concerning vitamin, mineral, and dietary properties of foods (sec. 403(j)); limitations on quantity of added poisonous or deleterious substances whose presence cannot be avoided by good manufacturing practice (sec. 406(a)); issuance of temporary permits governing manufacturing, processing, or packing so as to prevent contamination with micro-organisms (sec. 404(a)); prescribing appropriate tests on methods of assay to determine

strength, quality, or purity of drugs (sec. 501(b)); designation of drugs as habit-forming (sec. 502 (d)); directions on label as to use of drugs (sec. 502(f)); statements on label as to precautions necessary by reason of liability of drug to deterioration (sec. 502(h)); and listing of harmless coal-tar colors and certification of batches thereof for foods, drugs, or cosmetics (secs. 406(b), 504, and 604).

"Such regulations are not merely interpretive. They have the force and effect of law and must be observed. Their violation may result in the imposition of criminal penalties, or in the confiscation of the goods involved if shipped in interstate commerce, or in their exclusion from the country if imported." *Id.* at pp. 9-10.

When additional rule-making authority has been granted by subsequent amendments to the statute, Section 701(e) has been made applicable to such regulations or a comparable procedure has been provided. See, *e.g.*, Section 408 (21 U.S.C. § 346a) authorizing regulations relating to tolerances for pesticide chemicals used on raw agricultural commodities, and Section 409 (21 U.S.C. § 348) relating to permissible food additives.

Congress also made clear the nature and purpose of the hearing which it intended be afforded:

"If as a result of the hearing on any proposal the Secretary determines to issue, amend, or repeal the regulation, the action taken may be based only on substantial evidence of record at the hearing. Similarly, the action of the Secretary in failing to carry into effect any proposal for issuance, amendment, or repeal of a regulation set for hearing must rest on a like basis. In either instance de-

> tailed findings of the facts on which the action of the Secretary is based are required to be made public as a part of his order. It follows that if the order of the Secretary is to be valid, the Government must have placed in the record at the hearing its evidence in support of the action taken and thereby afford opportunity for persons affected to controvert viva voce the Government's evidence. While common law or jury trial rules of evidence need not be enforced at such a hearing, nevertheless it is essential to such a hearing that all the evidence on which the administrative officer acts be disclosed at the hearing and that the right to controvert viva voce be accorded. Cf. *Ohio Bell Tel. Co.* v. *Public Utilities Comm. of Ohio* (1937) 301 U.S. (preliminary print) 292." H.R. Rep. No. 2139, 75th Cong., 3d Sess. 9 (1938).

The legislative history of the hearing and review provisions of the Act were discussed at length by this Court in *Abbott Laboratories* v. *Gardner,* 387 U.S. 136 (1967). The Court's comments are instructive:

> "The provisions now embodied in a modified form in § 701(f) were supported by those who feared the life-and-death power given by the Act to the executive officials, a fear voiced by many members of Congress. The supporters of the special-review section sought to include it in the Act primarily as a method of reviewing agency *factual* determinations. For example, it was argued that the level of tolerance for poisonous sprays on apple crops, which the Secretary of Agriculture had recently set, was a factual matter, not reviewable in equity in the absence of a special statutory review procedure. Some congressmen urged that challenge to this type of determination should be in the form of a *de novo* hearing in a district court, but the

> Act as it was finally passed compromised the matter by allowing an appeal on a record with a 'substantial evidence' test, affording a considerably more generous judicial review than the 'arbitrary and capricious' test available in the traditional injunctive suit." 387 U.S. at 143.

The Court concluded that the special-review procedures provided in Section 701(f) were intended to assure adequate judicial review of agency decisions expressed in "regulations embodying technical factual determinations." *Id.* at p. 144.

Thus, both the terms of the statute and its legislative history make clear that the Congress specifically enumerated the nature of the legislative regulations which could be issued by the Commissioner, and required that such regulations be issued only after hearing and be subject to special provisions relating to judicial review. Congress did not delegate legislative authority to the agency to issue regulations making a legally binding determination as to whether a drug is a "new drug" or as to whether it is "misbranded." Both the terms of the Act and its administrative and judicial interpretation since its enactment show that such factual questions were intended to be decided by the courts.

The OTC review procedure also raises serious questions of due process. The Commissioner not only proposes to make a conclusive determination of a factual question, which determination shall be binding on courts and not subject to "collateral attack" in a subsequent criminal, seizure, or injunctive action, but also proposes to make such a binding factual determination without affording an evidentiary hearing.

The Commissioner's final order establishing the OTC review procedure specifically asserts that such an evidentiary hearing is not required:

> "Neither the Administrative Procedure Act nor due process of law requires an evidentiary hearing. 5 U.S.C. 553 provides for a notice of proposed rule making, reference to the legal authority, and disclosure of the substance of the proposed rule. The agency must then give interested persons an opportunity to participate in the rule making through submission of written data, views, or arguments, with or without an opportunity for oral presentation. An evidentiary hearing is required under the Administrative Procedure Act only when it is required by other statutes." 37 Fed. Reg. 9472.

The argument apparently is that no hearing is required in a proceeding of this kind because the Federal Food, Drug, and Cosmetic Act does not require it. The answer to this argument is that the Act does not require a hearing in a proceeding of this kind because it does not authorize a proceeding of this kind.

Notice and hearing in a proceeding before an administrative agency may often be necessary to comply with the constitutional requirement of due process even though the statute governing the proceedings does not require a hearing. 2 Am. Jur. 2d, Administrative Law § 399; *Wong Yang Sung* v. *McGrath*, 339 U.S. 33 (1950). As the court stated in *American Airlines* v. *Civil Aeronautics Board*, 359 F.2d 624 (D.C. Cir. 1966):

> "This court has indicated its readiness to lay down procedural requirements deemed inherent in the very concept of fair hearing for certain classes of cases, even though no such requirements had

been specified by Congress. Gonzalez v. Freeman, 118 U.S.App.D.C. 180, 334 F.2d 570 (1964); Pollack v. Simonson, 121 U.S.App.D.C. 362, 350 F.2d 740 (1965)." 359 F.2d at 632.

The court noted that the report of the Senate Judiciary Committee on the Administrative Procedure Act had observed that some cases "tend to be accusatory in form and involve sharply controverted factual issues. Agencies should not apply the exceptions [from the hearing requirement] in such cases, because they are not to be interpreted as precluding fair procedure where it is required." 359 F.2d at 632, n. 22.

Earlier decisions of this Court often explained when an evidentiary hearing was required by due process in terms of whether (1) the proceeding was "rule-making" and the agency was acting in a "legislative" capacity, or (2) the proceeding was "adjudication" and the agency was acting in a "judicial" capacity—due process requiring an evidentiary hearing in the latter case.[9] However, courts are increasingly recognizing that the governing distinction is whether the agency is determining or acting on the basis of "legislative facts" or "adjudicative facts."

The terminology was first suggested by Professor Kenneth Culp Davis,[10] who thus summarized the effect of prior court decisions in his treatise:

> "The true principle is that a party who has a sufficient interest or right at stake in a determination of governmental action should be entitled to an

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[9] See, *e.g.*, *The Assigned Car Cases*, 274 U.S. 564 (1927).

[10] Davis, "An Approach to Problems of Evidence in the Administrative Process," 55 Harv. L. Rev. 364, 404-407 (1942).

> opportunity to know and to meet, with the weapons of rebuttal evidence, cross examination, and argument, unfavorable evidence of adjudicative facts, except in the rare circumstance when some other interest, such as national security, justifies an overriding of the interest in fair hearing." 1 Davis, *Administrative Law Treatise*, § 7.02, p. 412 (1958).

Professor Davis describes the distinction as follows: "Adjudicative facts are the facts about the parties and their activities, businesses, and properties. * * * Legislative facts do not usually concern the immediate parties but are general facts which help the tribunal decide questions of law and policy and discretion." *Id.* at p. 413.

This distinction between adjudicative and legislative facts is illustrated by the decisions of this Court in *Londoner* v. *City & County of Denver,* 210 U.S. 373 (1908), and in *Bi-Metallic Inv. Co.* v. *State Bd. of Equalization*, 239 U.S. 441 (1915). The distinction was recognized in *Gonzales* v. *United States,* 348 U.S. 407, 412 (1955). In considering whether a party is entitled to know and to meet information used by a tribunal, the Court distinguished some cases on the ground that "they do not involve individualized fact finding and classification, but legislative determinations, political judgments, and the exercise of judicial discretion. . . ." 348 U.S. at 412. More recent cases in the lower courts have been more explicit in contrasting "legislative" and "adjudicative" facts. See, *e.g., Hornsby* v. *Allen,* 326 F.2d 605 (5th Cir. 1964); *American Airlines* v. *Civil Aeronautics Board,* 359 F.2d 624 (D.C. Cir. 1966); *Utica Mutual Ins. Co.* v. *Vincent,* 375 F.2d 129 (2d Cir. 1967); *U.S. Rubber Co.* v. *NLRB,*

373 F.2d 602, 605 (5th Cir. 1967); and *Powelton Civic Home Owners Assn.* v. *Dept. of Housing and Urban Development,* 284 F.Supp. 809 (E. D. Pa. 1968).[11]

The facts which the Commissioner purports to have authority to determine are clearly adjudicative. He proposes to determine whether a particular drug is generally recognized as safe or effective and whether its labeling is false or misleading. These are clearly "facts about the parties and their activities, businesses, and properties." Davis, *supra,* p. 46. They "involve individualized fact finding and classification." *Gonzales* v. *United States, supra,* p. 46. While "couched as rule making, general in scope," such a determination "in substance and effect is individual in impact and condemnatory in purpose." *American Airlines* v. *Civil Aeronautics Board, supra,* p. 46.

In fact, it is generally true that "the need for an evidentiary hearing [is] present when it is proposed to apply a statute couched in general terms. . . ." *Superior Oil Co.* v. *F.P.C.,* 322 F.2d 601, 614 (9th Cir. 1963), *cert. denied,* 377 U.S. 922 (1964). For example, in *Denver Union Stock Yard Co.* v. *Producers Livestock Marketing Association,* 356 U.S. 282, 287 (1958), this Court observed, "When an Act condemns a practice that is 'unfair' or 'unreasonable,' evidence is normally necessary to determine whether a practice, rule, or regulation transcends the bounds. See *Associated Press* v. *Labor Board,* 301 U.S. 103; *Chicago Board of Trade* v. *United States,* 246 U.S. 231; *Sugar Institute* v. *United States,* 297 U.S. 553." Thus, the determination

[11] The distinction has also been specifically adopted as the basis for the provisions concerning judicial notice in the "Rules of Evidence for United States Courts and Magistrates."

of whether a particular course of conduct is fraudulent or unfair, or a particular statement is false or misleading—one of the determinations being made in the OTC review—is a determination of "adjudicative facts," and an evidentiary hearing is required by due process. See, *e.g., U.S. Rubber Co.* v. *NLRB, supra,* p. 605; *S.E.C.* v. *Frank,* 388 F.2d 486 (2d Cir. 1968); *NLRB* v. *Smith Industries,* 403 F.2d 889 (5th Cir. 1968).

The necessity for an evidentiary hearing is also clear if one applies the traditional test in which private right is balanced against public purpose. As the Court stated in *Cafeteria & Restaurant Workers Union* v. *McElroy,* 367 U.S. 886, 895 (1961), "consideration of what procedures due process may require under any given set of circumstances must begin with a determination of the precise nature of the government function involved as well as of the private interest that has been affected by governmental action."

The rule-making involved in the OTC review seeks to bar from the market drugs whose margin of safety is such that they are permitted to be sold over the counter, rather than being required to be dispensed on prescription. Most have been on the market for many years, and were specifically exempted by the 1938 and 1962 "grandfather" clauses from the strict regulatory control applicable to most prescription drugs. Even the drugs so exempted have been subject since 1938 to being seized, condemned, and barred from commerce if their labeling was false and misleading in any respect. The rule-making authority being asserted by the FDA, if it exists at all, has existed since 1938. Clearly, there is no such urgency or public health hazard as would constitute "the rare circumstance

when some other interest . . . justifies an overriding of the interest in fair hearing." Davis, *supra,* p. 46.

As discussed *supra,* pp. 38-43, in those instances in which the Commissioner has been authorized by the Act to issue regulations making similar factual determinations, the Congress has consistently required that he afford affected parties an opportunity for an evidentiary hearing, and has provided for judicial review on the record of such hearing. Thus, even where more serious health hazards might be involved, Congress has not found an overbalancing public interest requiring that fair hearing be denied.

The clear trend of recent court decisions is to afford increasing protection to private rights by requiring an evidentiary hearing where the principal argument against it is, as here, one of administrative convenience. See, *e.g., Goldberg* v. *Kelly,* 397 U.S. 254 (1970); *Bell* v. *Burson,* 402 U.S. 535 (1971); *Escalera* v. *New York Housing Authority,* 425 F.2d 853 (2d Cir. 1970), *cert. denied,* 400 U.S. 853 (1970); and *Caulder* v. *Durham Housing Authority,* 433 F.2d 998 (4th Cir. 1970), *cert. denied,* 401 U.S. 1003 (1970). In fact, *Bell* has been read as broadly as holding "that where the government has issued a benefit to an individual, whatever that benefit may be, it will take more than administrative and fiscal considerations to suspend or terminate that benefit without a prior hearing." Project, Federal Administrative Law Developments—1971, 1972 Duke L. J. 115, 168.

III. Section 107(c) of the Drug Amendments of 1962 Neither Extends FDA's Authority Over Drugs Which Have Never Been the Subject of a New Drug Application Nor Terminates Its Authority To Withdraw Approval of a New Drug Application

A. The Provisions and Legislative History of Section 107(c) of the Drug Amendments of 1962

The Government, as petitioner in *Bentex* and as respondent in *Hynson* and *USV*, urges that paragraph (4) of Section 107(c) of the Drug Amendments of 1962 (Public Law 87-781, 76 Stat. 788-789, 21 U.S.C. § 321 note; Joint App. 481-482) operates to extend FDA's authority to cover drugs which have never been the subject of a New Drug Application. The cross-petitioner in *Hynson* apparently urges that the same paragraph terminates the FDA's authority to withdraw its approval of a New Drug Application. Both claims are completely unsupported, either by the literal terms of that paragraph or by the legislative history.

While it is possible in the case of every statute as complex as the Food, Drug, and Cosmetic Act and its 1962 Amendments to argue *ad infinitum* as to whether the statute carried out the express intentions of its sponsors, or whether their comments about it on the Senate or House floor accurately described its contents, the basic reference must necessarily be what the statute itself says. We submit that the provisions of Section 107(c) are neither complex nor obscure.

The 1938 Act prior to its amendment in 1962 had not provided for administrative approval of a New Drug Application; rather, it provided that such application "shall become effective" within a specified period after filing unless the Secretary should "issue an order refusing to permit the application to become

effective." § 505, 52 Stat. 1052; Joint App. 483-484. Section 107(c)(2) of the 1962 Amendments provides that such application "which was 'effective' within the meaning of that Act on the day immediately preceding the enactment date [of the amendments] shall be deemed as of the enactment date, to be an application 'approved' by the Secretary within the meaning of the basic Act as amended . . . ."

Section 107(c)(3) provides that "[i]n the case of any drug with respect to which an application . . . is deemed to be an approved application on the enactment date by virtue of paragraph (2)," the amendments with respect to effectiveness made in the definition of a "new drug" and in the provisions relating to approval of a New Drug Application shall not apply "so long as approval of such application is not withdrawn," unless new claims are made for the drug; and that the FDA may not withdraw approval of such application on grounds of lack of effectiveness for two years.

Section 107(c)(4) provides that the amendments to the definition of a "new drug" made by the amendatory statute shall not apply to any drug which on the day immediately preceding the enactment of the amendments "(A) was commercially used or sold in the United States, (B) was not a new drug as defined [in] the basic act as then in force, and (C) was not covered by an effective application under section 505 of that act."

The distinction apparently made by these provisions is between a drug previously marketed on the basis of proof of safety for which a New Drug Application "was 'effective'," on the one hand, and a drug previously marketed on the basis of the general recogni-

tion of its safety for which no New Drug Application was "effective," on the other hand. In other words, drugs legally on the market with a New Drug Application were to be governed by Section 107(c)(3), and drugs legally on the market without a New Drug Application were to be governed by Section 107(c)(4). That this was the distinction in fact intended by Congress is borne out by the legislative history.

Section 107(c) of the 1962 Amendments is identical to Section 8(g) of the bill S. 1552 as reported by the Senate Committee on the Judiciary on August 21, 1962. This was the third version of S. 1552. The bill originally introduced by Senator Kefauver was first reported by the Judiciary Committee substantially amended on July 19, 1962. It was the third version as reported by the committee on August 21, 1962, which was subsequently considered and passed by the Senate. The committee's report contained the following explanation of its amended Section 8(g), which became Section 107(c) in the statute as finally enacted:

> "Section 8 of the bill, dealing with 'effectiveness,' contained no transitional provisions relating to the application of these amendments to drugs already on the market.
>
> "The committee amendment would insert detailed transitional provisions. Under the amendment, *a drug which is on the market and has gone through the new-drug procedure* would not have to be resubmitted for clearance of existing label claims with respect to effectiveness of the drug unless approval of the new drug is withdrawn or suspended under the act or unless an amendment or supplement to the effective new-drug application is filed (in which event only the changed labeling would be reevaluated).

"Secondly, under this transitional provision the new grounds for withdrawing approval of a new drug already on the market under the new authority relating to drug effectiveness would not apply until 2 years after the bill is enacted unless approval of the new drug is withdrawn or suspended earlier on other grounds.

"Thirdly, in the case of *a drug on the market which was never subject to the new-drug procedure* before, the amendments to the new-drug definition relating to drug effectiveness would not apply to existing labeling claims." (Emphasis added.) S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess. 7-8 (1962).

The "Statement of the Managers on the Part of the House" included in the Conference Report shows that the House conferees agreed to the Senate language on the basis of the same understanding of its meaning:

"The Senate version, with respect to amendments relating to the effectiveness of drugs, contained provisions preventing their application to *previously approved drugs* except with respect to changed uses or conditions of use recommended in their labeling, so long as approval of the application is not suspended or withdrawn. The Senate version also provided that until either the expiration of 2 years after the enactment of the bill, or until the effective date of an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act withdrawing or suspending the approval of an application, the new 'lack of substantial evidence of effectiveness' test for withdrawal of new-drug approval shall not apply.

"The conference substitute adopts the Senate version and also contains the Senate language providing with respect to existing labeling claims of *drugs that have never previously been subject to*

will not be affected by the new effectiveness test insofar as their existing claims are concerned." 108 Cong. Rec. 17366, quoted in Brief for Petitioners, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.*, No. 72-555, p. 14, fn. 32. Senator Kefauver, the author of the original bill, speaking next on the Senate floor, stated that the Chairman "has accurately defined the provisions of the substitute which was reported on August 21." 108 Cong. Rec. 17367.

The most that can be said for the FDA's contention is that it must mark a new high in agency ingenuity. Obviously drugs which were never covered by an application at all—*i.e.*, drugs for which no application was ever filed and thus for which no application could possibly become "effective"—were "not covered by an effective application." As the Court of Appeals stated in its opinion in *USV*, drugs "which were generally recognized as safe and were marketed as 'old drugs' without an approved NDA on October 9, 1962, * * * [meet] literally the criteria for exemption stated in the 'grandfather clause.'" *USV Pharmaceutical Corporation* v. *Richardson*, 461 F.2d 223, 228 (4th Cir. 1972); Joint App. 470.

The total invalidity of the Government's theory on the basis of the structure of the statute, the specific provisions and history of Section 107(c)(4), the agency's consistent and contrary interpretation over many years, and the procedural and due-process problems it would create have all been thoroughly treated in the Brief for Petitioner in No. 72-666, *USV Pharmaceutical Corporation* v. *Weinberger*, pp. 26 *et seq.* There is no need for *amicus* to repeat these arguments. However, several additional comments are appropriate.

What the agency attempted in *Bentex* and *USV* was similar to the process which this Court condemned in *NLRB* v. *Wyman-Gordon Co.*, 394 U.S. 759 (1969). The FDA attempted to make rules of "general . . . applicability and future effect" in an adjudicatory proceeding, without complying with the procedural requirements for rule-making imposed by 5 U.S.C. § 553. The FDA sought to make generally applicable to all manufacturers a factual determination with respect to a particular drug made in an adjudicatory proceeding to which only that drug's manufacturer was a party. This Court's comments in *Wyman-Gordon* are applicable:

> "The rule-making provisions of that Act, which the Board would avoid, were designed to assure fairness and mature consideration of rules of general application. * * * They may not be avoided by the process of making rules in the course of adjudicatory proceedings. There is no warrant in law for the Board to replace the statutory scheme with a rule-making procedure of its own invention. Apart from the fact that the device fashioned by the Board does not comply with statutory command, it obviously falls short of the substance of the requirements of the Administrative Procedure Act." 394 U.S. at 764.

After these cases arose, the FDA recognized the necessity to comply with the basic notice provisions of the Administrative Procedure Act. On October 31, 1972, it adopted a new regulation as § 130.40 of Title 21 of the Code of Federal Regulations, entitled "Applicability of Drug Efficacy Study Implementation Notices and Notices of Opportunity for Hearing to Identical, Related, and Similar Drug Products." 37 Fed. Reg. 23187.

Subsection (a) of the new 21 C.F.R. § 130.40 states:

> "The Food and Drug Administration's conclusions on the effectiveness of drugs are currently being published in the Federal Register as Drug Efficacy Study Implementation (DESI) Notices and as Notices of Opportunity for Hearing. The specific products listed in these notices include only those that were introduced into the market through the new-drug procedures from 1938-62 and were submitted for review by the National Academy of Sciences-National Research Council (NAS-NRC), Drug Efficacy Study Group. Many products which are identical to, related to, or similar to the products listed in these notices have been marketed under different names or by different firms during this same period or since 1962 without going through the new-drug procedures or the Academy review. Even though these products are not listed in the notices, they are covered by the new drug applications reviewed and thus are subject to these notices. All persons with an interest in a product that is identical, related, or similar to a drug listed in a drug efficacy notice or a notice of opportunity for a hearing will be given the same opportunity as the applicant to submit data and information, to request a hearing, and to participate in any hearing."

Of course, the agency's recent attempt to comply with the Administrative Procedure Act does not cure the basic defect that non-NDA'ed drugs were not "covered by the new drug applications reviewed," and thus are entitled to the protection of Section 107(c)(4). However, serious problems would be presented, even were the Court to adopt the Government's bizarre interpretation of the latter section. The new regulation continues:

> "It is not feasible for the Food and Drug Administration to list all products which are covered by

an NDA and thus subject to each notice. However, it is essential that the efficacy conclusions be applied to all identical, related, and similar drug products to which those conclusions are reasonably applicable. Any product not in compliance with an applicable drug efficacy notice is in violation of section 505 (new drugs) and/or section 502 (misbranding) of the act. * * * Where experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs would conclude that the findings in a drug efficacy notice or notice of opportunity for hearing concerning effectiveness are applicable to an identical, related, or similar drug product, such product is affected by the notice. A combination drug product containing an identical, related, or similar drug is also subject to the conclusions contained in the notice."

What this illustrates is that the whole concept of "me-too" drugs is so imprecise and speculative that no adequate notice is really possible. "Identical" is a precise adjective. "Similar" is less precise. "Related" is vaguer still. But to regard a "combination drug product containing an identical, related, or similar drug" as one of its ingredients as a "me-too" drug stretches the concept to include almost everything. In fact, the FDA's new theory has been asserted to deny the marketability of a drug, none of the ingredients of which are the same as those in the "pioneer drug" subject to the NDA, but which is intended for the same therapeutic purposes.

The Government explains the FDA's motivation for devising its new interpretation of the statute as follows:

"The agency believed that it would be inconsistent and unjust to drug manufacturers and to the

> public to construe the Act as requiring manufacturers of the 'pioneer' drugs, who had filed an NDA, to produce substantial evidence of effectiveness or lose their marketing approval, while at the same time permitting 'me-too' drugs, which owed their marketability to the pioneer NDAs, to remain on the market without demonstrating effectiveness." Brief for Petitioners, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.*, No. 72-555, p. 19.

It should be observed, *first,* that the agency's belief that the 1962 Amendments produced "inconsistent and unjust" results does not justify the Act's judicial amendment to produce a result directly the opposite of that which the statute commands. Such amendment is properly sought in the Congress. *Second,* drugs on the market without an approved New Drug Application do not "[owe] their marketability to the pioneer NDAs." Those which were on the market prior to 1962 "owe their marketability" to the general recognition of their safety. Those introduced since 1962 "owe their marketability" to the general recognition of their safety and effectiveness. If they lack the requisite general recognition, or if their labeling is false or misleading, they are subject to seizure, their distribution can be enjoined, and their manufacturers are subject to criminal penalties.

The fact that non-NDA'ed drugs are subject to these sanctions suggests that there is nothing "inconsistent and unjust" inherent in the provisions of the Act, but only in the way that the Government chooses to describe them. As discussed *infra,* pp. 70-72, there is no question that drugs marketed under an NDA are required to meet a higher standard, particularly with reference to proof of effectiveness, than are non-NDA'ed drugs. However, they also benefit from significant protective provisions. It is in this light, too, that

Section 505(e) should be viewed. For example, Section 505(e), as amended in 1962, provides an administrative alternative to seizure or injunction to correct false and misleading labeling of an NDA'ed drug. This provision is thus described in the Senate Report on the 1962 Amendments:

> "The proposed committee amendment would also amend the provision in the bill which directs the Secretary to withdraw a new-drug approval if he finds that the labeling is false or misleading by placing the provision among the discretionary provisions for withdrawal, and would permit withdrawal of approval only if the labeling was not corrected within a reasonable time after notice from the Secretary. This would give greater flexibility to the Food and Drug Administration and give the manufacturer an opportunity to remedy the defect before withdrawal action is taken." S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess. 7 (1962).

Thus, not only is the inconsistency one which Congress knowingly created, but also it is not as unjust as the Government suggests.

C. Section 107(c) of the Drug Amendments of 1962 Does Not Exempt a Drug Which Has Been the Subject of a New Drug Application From an Administrative Proceeding To Withdraw Approval of That Application

As *amicus* has already emphasized, *Hynson* presents a different question from that presented in *Bentex,* because the drug involved in *Hynson* had been the subject of a New Drug Application and the issue between the manufacturer and the FDA arose as the result of the FDA's instituting an administrative proceeding to withdraw approval of the NDA which had "become effective" prior to 1962.

Faced with a notice of the FDA's intention to withdraw approval of the NDA covering its drug, the manufacturer in *Hynson* first filed an action for a declaratory judgment seeking a judicial determination as to whether the drug was still a "new drug." The District Court held that the issues presented were within the primary jurisdiction of the FDA and that the manufacturer had failed to exhaust its administrative remedies, and dismissed the action. No appeal was taken. Instead, the manufacturer asked for a hearing on the issue in the administrative proceeding to withdraw approval of the NDA. The FDA denied the request for a hearing and issued a final order of withdrawal. The Court of Appeals reversed, on the ground that the FDA was required to hold a hearing on a question not directly relevant here. The manufacturer, as cross-petitioner in No. 72-414, argues that in the hearing on whether to withdraw approval of the NDA, the FDA must first determine whether the drug involved is exempt from administrative withdrawal proceedings because of the provisions of Section 107(c) of the 1962 Amendments. Thus *Hynson* presents the question whether the manufacturer is entitled to an administrative determination of that question in a proceeding to withdraw approval of an NDA.[12]

The contention of the cross-petitioner in *Hynson*, that it is entitled to an initial determination in an administrative proceeding to withdraw the NDA as to whether its drug is exempt from such proceedings because of Section 107(c) of the 1962 Amendments, is

[12] The manufacturer in *Hynson* also argues that in the proceeding to withdraw approval of the NDA it is entitled to an administrative determination as to whether the drug is generally recognized as safe and effective. This question is discussed *infra*, pp. 65 *et seq.*

disposed of easily. This Court should determine as a matter of law that Section 107(c) cannot exempt a drug from administrative proceedings to withdraw approval of its NDA. This result is compelled by the structure of the "grandfather" clause. The only limitations placed by Congress on the right of the FDA to withdraw its approval of an NDA are contained in Section 107(c)(3), the paragraph applicable to drugs for which such application had been filed. No limitations were placed on the FDA's right to withdraw an NDA in Section 107(c)(4), because by its terms it does not apply to drugs subject to an NDA.

The Court of Appeals in its opinion in *USV* concluded: "The Congress never intended that a drug being marketed under an approved NDA might qualify under the 'grandfather clause.' This is plain from the comment in the Conference Committee Report that the exemption was to apply 'to existing labeling claims of drugs *that have never previously been subject to the new-drug procedure'*. (Italics added.)" *USV Pharmaceutical Corporation* v. *Richardson,* 461 F.2d 223, 227 (4th Cir. 1972); Joint App. 470. As discussed *supra,* pp. 50-54, this is obviously a correct reading of the legislative history.

This interpretation of Section 107(c), in addition to being compelled by its literal terms and history, has the virtue of eliminating further protracted controversy, either in the courts or in administrative proceedings, as to the status of drugs marketed before 1962. A given drug was either marketed pursuant to a New Drug Application or it was not. If it was, its "grandfather" rights are fixed by Section 107(c)(3). If it was not, its "grandfather" rights are fixed by Section

107(c)(4). No drug is exempted from a proceeding to withdraw approval of its NDA by Section 107(c). If a drug has been the subject of an NDA it is not covered by Section 107(c)(4), and the two-year moratorium granted by Section 107(c)(3) has expired.

The cross-petitioner in *Hynson* argues that in the administrative proceeding to withdraw its NDA the FDA must determine, after a hearing required by due process, whether the drug involved "is exempt from *administrative* withdrawal proceedings because of Section 107(c)(2) of the 1962 Amendments or from both *administrative* and *judicial* withdrawal proceedings by reason of Section 107(c)(4) of the amendments . . . ." Brief of Cross-Petitioner, *Hynson, Westcott and Dunning, Incorporated* v. *Weinberger*, No. 72-414, p. 12. If by "withdrawal proceedings" the cross-petitioner means a proceeding to withdraw approval of the NDA, it follows from the foregoing discussion that (1) nothing is exempted from anything by Section 107(c)(2); (2) no drug which was marketed pursuant to an NDA is exempted from administrative proceedings to withdraw that NDA by Section 107(c)(4); and (3) there are no "judicial withdrawal proceedings" provided in the Act from which to be exempted.

If by "withdrawal proceedings" the cross-petitioner means any proceeding which would result in his having to "withdraw" the drug from the market—*i.e.*, civil actions to seize and condemn the drug or enjoin its distribution—it obviously is not "exempt" from such proceedings, although if its drug is "generally recognized as safe and effective" it may have the right to continue to market the drug. It is this question which *amicus* will next discuss.

IV. The FDA's Statutory Authority To Withdraw a New Drug Application Does Not Depend on a Prior Determination That the Subject Drug Is Not Generally Recognized as Safe and Effective

A. Introduction

Both the drug involved in *Hynson* and that involved in *CIBA* had been the subjects of New Drug Applications, and the issues as to their marketability arose as a result of the FDA's instituting administrative proceedings to withdraw its prior approvals of the NDA's involved. However, there are significant differences between the issues posed in *Hynson* and those in *CIBA*.

As discussed *supra,* p. 62, the manufacturer in *Hynson* sought a hearing before the agency. The FDA denied its request for hearing and issued a final order withdrawing approval of the NDA. Although the Court of Appeals reversed, the manufacturer here argues that on remand the FDA should be required to determine whether its drug is still a "new drug" under the Act. It argues that if its drug has become "generally recognized as safe and effective" it is no longer a "new drug," and seems to conclude from this that the agency has no authority to withdraw its prior approval of the NDA. In any event, it argues for an administrative determination of the question of new-drug status.

The manufacturer in *CIBA* filed an action for a declaratory judgment determining whether its drug is still a "new drug." Before the cause was heard in the District Court, the FDA's order withdrawing approval of the NDA had been issued. The District Court then dismissed the declaratory judgment action on the ground that even if it had jurisdiction it would exercise its discretion and refuse to determine whether the drug was a "new drug." The Court of Appeals affirmed the

dismissal. The manufacturer complains of this action and seeks to have the case remanded to the District Court. Thus *CIBA* presents the question whether the manufacturer is entitled to a judicial determination, after an NDA has been withdrawn, as to whether its drug is no longer a "new drug," and so can be legally marketed despite the withdrawal of the NDA.

The "threshold question" presented by these cases is not a factual one but a legal one: Whether a drug which was once a "new drug," and was originally marketed pursuant to a New Drug Application, may subsequently become "generally recognized as safe and effective" and thus cease to be a "new drug." The latter construction has been adopted by officials of the FDA in the past and appears to be accepted by the Government.

If a drug's new-drug status is permanently established for regulatory purposes when it is first marketed under an NDA, there can be no question that the FDA has authority, upon proper findings, to withdraw approval of the NDA. If, as a matter of law, the only inquiry is whether a New Drug Application ever became effective or was approved, the issue of new-drug status clearly does not arise in the administrative proceeding to withdraw that approval, nor does it arise in a subsequent judicial proceeding. The drug is simply a "new drug," without an approved NDA, and cannot be legally marketed.

If, on the other hand, the regulatory status of a drug originally marketed pursuant to an NDA can subsequently change if it becomes "generally recognized as safe and effective," the subsidiary questions posed in *Hynson* and *CIBA* do arise. We assume, *arguendo*, that they do.

B. The Issue in Hynson

The question whether a drug has become "generally recognized as safe and effective" is not an issue in a proceeding to withdraw approval of the earlier NDA unless such general recognition terminates the authority or responsibility of the FDA to withdraw such approval. We believe that the proper construction of the statute is that the subsequent general recognition of a drug's safety and effectiveness does not affect the withdrawal proceeding and is not an issue in such proceeding.

The provisions of Section 505(e), 21 U.S.C. § 355(e), are by their terms mandatory. The section provides: "The Secretary *shall* . . . withdraw approval of an application with respect to a new drug under this section if the Secretary finds (1) . . . that such drug is unsafe . . . ; (2) . . . that such drug is not shown to be safe . . . ; (3) . . . that there is lack of substantial evidence that the drug will have the effect it purports or is represented to have . . . ; or (4) that the application contains any untrue statement of a material fact."

While the statute provides that if any of these four findings are made the Secretary "shall . . . withdraw approval," in other situations his action is discretionary. The section continues: "The Secretary *may* also . . . withdraw the approval of an application" if he finds that the applicant has failed to maintain adequate records or to make required reports, or if he finds inadequacies in the methods, facilities, or controls used by the manufacturer, or if he concludes that the labeling of such drug is false or misleading and this is not corrected after reasonable notice.

Congress was fully aware of the distinction made in the section between those circumstances in which withdrawal of approval was mandatory and those in which it was discretionary. The Senate Report on the 1962 Amendments states: "The proposed committee amendment would also amend the provision in the bill which directs the Secretary to withdraw a new-drug approval if he finds that the labeling is false or misleading by placing the provision among the discretionary provisions for withdrawal. . . ." S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess. 7 (1962).

Nothing in the Act provides that, if the drug has become "generally recognized as safe and effective," the agency is relieved of its mandatory duty to withdraw approval of an NDA. Moreover, the fact that Congress in the 1962 Amendments placed a specific limitation on the agency's right to withdraw approval argues that it intended no such general limitation as that being considered here. Section 107(c)(3)(B) provided that clause (3) of the first sentence of Section 505(e), requiring withdrawal of approval of an application if the Secretary finds that there is a lack of substantial evidence of effectiveness, should not apply to a drug subject to an effective NDA on the date of the amendment until two years after the amendment, or until approval was withdrawn on other grounds than those of lack of effectiveness. § 107(c) of Public Law 87-781, 76 Stat. 788-789 (1962), 21 U.S.C. § 321 note; Joint App. 482. Nothing suggests that Congress intended any further limitation on the agency's authority.

Since the 1962 Amendments became fully effective, in order to obtain approval of an NDA and in order to retain that approval the manufacturer must submit "substantial evidence that the drug will have the effect it purports or is represented to have." § 505(d)(5) and

(e)(3), 21 U.S.C. § 355(d)(5) and (e)(3). As used in those subsections, " 'substantial evidence' means evidence consisting of adequate and well-controlled investigations including clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have. . . . " § 505(d), 21 U.S.C. § 355(d).

From the time that the bill as passed was originally reported in 1962, this new standard has been cited as one of the major changes made by the 1962 Amendments. The history of the requirement of "substantial evidence" in those amendments is reviewed in the Government's Brief for Petitioners in No. 72-394, *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, at pp. 14-17. The Government concludes: "Thus the history of the 'substantial evidence' provisions of the Act shows increasingly stringent statutory language culminating in the provision that is now the law." *Id.* at p. 17.

Originating in recommendations from the medical and scientific community, this change ultimately involved a substantial segment of that community in the massive Drug Efficacy Study conducted for the FDA by the National Academy of Sciences-National Research Council. It is implicit in the history of the 1962 Amendments and in the sweeping review of drugs which was instituted following their enactment that the medical and scientific community is entitled to assume that if the NDA covering a particular drug has not been withdrawn it is because that drug meets the new stringent standard for proof of effectiveness. It would be a strange result indeed if, in the absence of sub-

stantial evidence of effectiveness, the agency could still not withdraw its approval of the NDA because the drug meets the different standard involved in "general recognition of safety and effectiveness."

That it is a different standard is well-settled. The nature of the difference is clearly stated in the opinion of the Court of Appeals in *Bentex:*

> "[W]hen filed, the application puts in issue only one question: Is the article safe and effective? That and that alone is the issue to be considered by the Secretary in connection with an application for approval filed by a manufacturer under Section 355(d), 21 U.S.C. That issue is quite different from that presented when there is an issue whether a drug fits the statutory definition of 'new drug' in the Act. The criterion for ascertaining whether a product is within statutory definition of 'new drug' under the Act is not safety and effectiveness *per se,* which, as we have observed, is the issue before the Secretary in connection with application for approval of a 'new drug', but 'whether the government has shown by a preponderance of the evidence that the "drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof."' " 463 F.2d 363, 371-372; Joint App. 268-269.

As the court observed in *United States* v. *Article of Drug, etc.,* 415 F.2d 390, 392 (5th Cir. 1969), in determining whether a drug is generally recognized as safe and effective, "the nature of expert opinion about [the drug], and not its actual safety or effectiveness, is the ultimate fact issue."

Moreover, the issue as to whether there is general recognition of a drug's safety and effectiveness does not involve the kind of scientific expertise required to determine whether a clinical study is "adequate and well-controlled." Rather, as the Court of Appeals observed in *Bentex,* whether a drug is generally recognized as safe and effective "is an issue that must be and is resolved, sometimes with, and at other times without a jury, in practically every injunctive, seizure, or criminal proceeding under the Act." 463 F.2d at 372; Joint App. 269.

The Government, attempting to support its claim that determination of general recognition should be shifted from the courts to the agency, asserts in its brief in *Bentex:*

> "Indeed, it is the position of FDA that as a general proposition there can be no general recognition of safety and effectiveness by experts where 'substantial evidence' of effectiveness as defined by Congress is lacking. In other words, the kind of scientific support for claims of efficacy required to obtain approval of an NDA is generally a necessary condition to avoidance of 'new drug' status (although not necessarily a sufficient condition, since a drug can be proved efficacious without there being a general recognition of this fact), so that a major part of the inquiry under both Section 201(p) and Section 505(d) is precisely the same." Brief for Petitioners, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.,* No. 72-555, p. 57.

This attempt to reverse all prior court pronouncements on the question finds no support either in the statute or the legislative history. By the terms of Section 505(d) it is only "as used in this subsection [(d)]

and subsection (e)" that " 'substantial evidence' means evidence consisting of adequate and well-controlled investigations." Moreover, the legislative history of the 1962 Amendments confirms that the "substantial evidence" requirement was applicable only to the approval or withdrawal of approval of an NDA. See, for example, the comments of Senator Eastland summarizing the bill as Chairman of the Judiciary Committee in 108 Cong. Rec. 10366 (1962) quoted *supra,* pp. 55-56.

Therefore, we submit that the FDA's authority and duty to withdraw approval of a New Drug Application is not affected by general recognition of the drug's safety and effectiveness. It follows that the issue, as to whether there is general recognition of a drug's safety and effectiveness, does not arise in a proceeding to withdraw approval of the NDA. Contrary to the view of the Court of Appeals in *CIBA* (463 F.2d 225; Joint App. 216), there is no "threshold question" or "jurisdictional issue" as to "whether the product in question in a given case is lawfully subject to such proceeding."

The Government, as petitioner in *Hynson,* devotes a substantial part of its brief to justifying the necessity and legality of its regulations requiring that there be a genuine and substantial issue of fact before it will grant a hearing prior to withdrawal of approval of an NDA. Brief for Petitioners in No. 72-394, pp. 14-24. Yet it urges affirmance of *CIBA,* holding that the question of whether a drug is generally recognized as safe and effective is a "jurisdictional issue" which determines "whether the product in question in a given case is lawfully subject to such proceedings." If this view were adopted, it would mark the virtual end of the

agency's "summary judgment" procedure in withdrawal proceedings.

As discussed *supra,* pp. 45-48, whether a drug is generally recognized as safe and effective involves adjudicative facts, which due process requires be decided only after an evidentiary hearing. Even were the Government to prevail in its argument as petitioner in *Hynson* that the burden is on the manufacturer to show a *prima facie* case in order to gain a hearing, is not that burden met by the affidavit of a single expert attesting that the drug involved is generally recognized as safe and effective?[13]

If, as the Government insists, it can only discharge its obligations under the Act if it can bar at the threshold applications for hearing which raise no substantial and material issue of fact, then effective enforcement as well as the literal terms of the statute require that the agency's right to withdraw approval of an NDA should not depend upon a prior determination as to whether there is general recognition of the drug's safety and effectiveness.

C. The Issue in CIBA

If, then, general recognition is not an issue in the withdrawal proceeding, and the NDA has been withdrawn, does the manufacturer have a right to continue to market the drug if it is generally recognized as safe

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[13] In fact, the obligation is on the Commissioner to make a *prima facie* case for denial of the hearing. *USV Pharmaceutical Corp.* v. *Richardson,* 466 F.2d 455 (D.C. Cir. 1972). The Government did not seek this Court's review of that decision of the Court of Appeals for the District of Columbia Circuit, but seeks its *de facto* reversal as petitioner in No. 72-394.

and effective, even though he lacks "substantial evidence of effectiveness" in the form of "adequate and well-controlled clinical studies"? The structure of the Act has led the agency and manufacturers to conclude in the past that he could. If the drug is generally recognized as safe and effective, it is not a "new drug" as defined in the Act. If it is not a "new drug," its introduction or delivery for introduction into interstate commerce without approval of an application filed under Section 505(b) is not prohibited by Section 505(a).

We submit therefore that the question presented to the District Court in a declaratory-judgment or enforcement proceeding is not one of law but one of fact: "whether the Government has shown by a preponderance of the evidence that the drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof." *Supra*, p. 70. Clearly the Government's burden is substantially lessened if it is armed with an adverse NAS-NRC report, but nothing in the Act precludes the District Court, as a matter of law, from deciding that there is general recognition of safety and effectiveness despite the absence of "adequate and well-controlled clinical studies."

As the court observed in *Bentex*, this "is manifestly a justiciable issue and the plaintiffs are entitled to a judgment on that issue by the Court, which alone has the jurisdiction to resolve it." 463 F.2d 363, 372; Joint App. 269. The petitioner in *CIBA* was entitled to such a determination in the District Court, and that court's dismissal of the declaratory-judgment action was an

abuse of discretion. The case should be remanded to the District Court for such a determination.

In fact, *CIBA* is a case which perfectly illustrates the wisdom of the Court's withholding its ultimate decision until the issue is presented in a case in which the lower courts have applied the law to facts fully developed in the record. The case presents the question of the right to continue to market a once-new drug, which is generally recognized as safe and effective, after its NDA is withdrawn; and on this question the lower courts have not yet spoken. It is an appropriate circumstance for application of Mr. Justice Jackson's terse phrase: "Of course, we will not undertake to review what the court below did not decide." *Walters* v. *City of St. Louis,* 347 U.S. 231, 233 (1954).

D. The Issue in USV

The issue as to the NDA'ed drugs involved in *USV* is similar to that in *CIBA,* but there are significant distinctions between the two cases. In *USV* the District Court *did* decide, after trial, that the NDA'ed drugs were not "new drugs" and thus could be marketed without an NDA. It found that the NDA'ed drugs were generally recognized as safe, held that general recognition of safety was all that was required, and did not decide whether the drugs were also generally recognized as effective. Joint App. 465.

The District Court did not reach the latter question because it held that *by operation of Section 107(c)(4) of the 1962 Amendments* all of the drugs involved in *USV,* including those originally marketed under an NDA, are entitled to be marketed without an NDA if they were generally recognized as safe and hence not a "new drug" prior to the 1962 Amendments. Clearly

this is correct as to the non-NDA'ed drugs. If no New Drug Application were ever filed, there was no application to "become effective," and the drugs were "not covered by an effective application" on October 9, 1962. However, the District Court also held that, while the NDA'ed drugs "were all covered [by effective New Drug Applications] at one time," those "applications . . . were withdrawn prior to October of 1962." Joint App. 464.

The Court of Appeals reversed both holdings. While accepting the trial court's view that a drug for which no NDA was ever filed met the requirements of Section 107(c)(4), the Court of Appeals held that if a manufacturer marketed one drug under an effective NDA its similar non-NDA'ed drugs were "covered" by that application. In this it was in error. As the Government now concedes, the same rule must apply to all non-NDA'ed drugs, regardless of their manufacturer.

The Court of Appeals also reversed the holding as to the NDA'ed drugs, on the ground that Section 107 (c)(4) does not apply to drugs which have been the subject of an NDA. As discussed *supra,* pp. 61-64, *amicus* believes that this holding is generally correct. However, the petitioner in *USV* argues that there are two circumstances, rather than only one, under which a drug should be held "not covered by an effective application under § 505": *first,* the obvious one in which no application was ever filed, and there was thus no application to "become effective"; and, *second,* where an application was filed and became effective, but had been withdrawn by the manufacturer with the concurrence of the FDA. The trial court found that the second

circumstance had, in fact, occurred in the case of the NDA'ed drugs involved in *USV*.

The Court of Appeals held that a proceeding under Section 505(e) was the only one provided in the Act by which the FDA could *withdraw its approval* of the NDA. However, this is a different question from whether the Act permits a manufacturer, with the concurrence of the FDA, to *withdraw its application*. On this question, *amicus* expresses no opinion.

However, for the reasons already treated at length, even if the view urged by the petitioner in *USV* is accepted, it would affect only the manufacturer's right to market the drug without an NDA, and would not affect the agency's right and duty to withdraw its prior approval of the earlier NDA if the requisite findings were made. The manufacturer's right to market the drug without an NDA, whether on a showing of general recognition of safety, or on a showing of general recognition of safety and effectiveness, is a question for the courts.

CONCLUSION

In No. 72-555, *Weinberger* v. *Bentex Pharmaceuticals, Inc., et al.*, the Court should affirm the decision of the Court of Appeals for the Fourth Circuit holding that the Food and Drug Administration does not have statutory authority to make a legally binding determination as to whether a drug which has never been the subject of a New Drug Application is a "new drug" as that term is defined in the Federal Food, Drug, and Cosmetic Act.

In No. 72-666, *USV Pharmaceutical Corporation* v. *Weinberger*, the Court should affirm that part of the decision of the Court of Appeals for the Fourth Cir-

cuit holding that a drug which has never been the subject of a New Drug Application "was not covered by an effective application," as that phrase is used in Section 107(c)(4)(C) of the Drug Amendments of 1962, even though an identical, similar, or related drug may have been marketed under an effective or approved New Drug Application.

The Court should reverse that part of the decision holding that a drug which has never been the subject of a New Drug Application was covered by an effective application, and thus not entitled to the exemption granted under Section 107(c)(4), if the identical, similar, or related drug was marketed under an effective or approved New Drug Application filed by the same manufacturer.

The Court should also affirm that part of the decision holding that the drugs marketed under New Drug Applications which became effective prior to the 1962 Amendments are not entitled to the exemption granted under Section 107(c)(4) of the amendments; unless the Court holds that a manufacturer can withdraw its application with the concurrence of the FDA, and had done so in this case, so that the subject drugs were not covered by an effective application on October 9, 1962.

In No. 72-414, *Hynson, Westcott and Dunning, Incorporated* v. *Weinberger,* the Court should affirm the decision of the Court of Appeals for the Fourth Circuit holding that the drug was marketed under a New Drug Application which became effective prior to the 1962 Amendments and is not entitled to the exemption granted under Section 107(c)(4) of the amendments, and, on remand of the case to the agency for a hearing,

limiting the issue to whether there is "substantial evidence" of effectiveness.

In No. 72-528, *CIBA Corporation* v. *Weinberger*, the Court should reverse the decision of the Court of Appeals for the Third Circuit and remand the case to the District Court for a determination as to whether the drug involved is generally recognized as safe and effective and thus entitled to be marketed despite the FDA's withdrawal of its approval of the New Drug Application.

Respectfully submitted,

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April 3, 1973

APPENDIX

The Proposed Procedures for Regulation of Over-the-Counter Drugs

A. The Purpose and Method of the Regulations

In his original proposal published for comment on January 5, 1972 (37 Fed. Reg. 85 *et seq.*), the Commissioner thus described the theory and purpose of the proposed regulations:

> "The Food and Drug Administration intends to require that all unapproved new drugs and misbranded drugs either be reformulated and/or relabeled to meet all requirements of the act or be removed from the market. In carrying out its responsibilities in this area, the Food and Drug Administration may either initiate a separate court action with respect to each violative OTC drug or deal with all OTC drugs through rulemaking by therapeutic classes on an industrywide basis. It has been determined that the latter approach should be pursued. * * *
>
> "Accordingly, the Commissioner proposes to establish procedures for rule making which will result in classifying some OTC drugs as generally recognized among qualified experts as safe and effective and not misbranded under prescribed, recommended, or suggested conditions of use. Any OTC drug not meeting the requirements established for such drugs pursuant to this procedure will have to be the subject of an approved new-drug application prior to marketing. (Since a grandfathered drug that is found to be misbranded would be required to change its formulation and/or labeling and thus lose its grandfathered status, any such product must either meet the applicable monograph or be the subject of an approved new-drug application in order to be legally marketed.) A deviation from a monograph will be approved for an individual

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manufacturer through approval of a new-drug application justifying such a deviation. Shipment of a nonconforming OTC drug (one neither classified as generally recognized as safe and effective and not misbranded, nor subject to an approved NDA) in interstate commerce will be prohibited. Responsible persons and the manufacturer and distributor will be subject to criminal prosecution and injunctive action, and the drug will be subject to seizure and injunction on the ground that the drug is an unapproved new-drug or is a misbranded drug (if it is exempt from the new-drug definition under the 1938 or 1962 grandfather clause)." 37 Fed. Reg. 86 (1972).

B. The Procedure To Be Followed

The procedure by which monographs are to be issued is set forth in subsection (a) of the final order. 21 C.F.R. § 130.301(a), 37 Fed. Reg. 9473 *et seq.* (1972). The Commissioner will first appoint an advisory review panel "of qualified experts" to evaluate the safety and effectiveness of each category of OTC drugs enumerated in subsection (b). § 130.301(a)(1), 37 Fed. Reg. 9473. Interested persons will be allowed to submit in specified form, for review and evaluation by the advisory review panel, published and unpublished data and information pertinent to the category of drugs or any marketed drug within the class. §130.301 (a)(2), 37 Fed. Reg. 9473-74. Any interested person may also request an opportunity to present oral views to the panel, but the order states that "such request may be granted or denied by the panel." § 130.301(a)(3), 37 Fed. Reg. 9474.

Following review of data submitted to it, the advisory review panel will prepare and submit to the Commissioner a report containing its conclusions and recommendations with respect to the conditions under which OTC drugs falling within the designated category are generally recognized as safe and effective and not misbranded. § 130.301(a)(5),

37 Fed. Reg. 9474. Included within the report will be a recommended monograph or monographs covering the category of OTC drugs and establishing conditions under which the drugs involved are generally recognized as safe and effective and not misbranded. The monograph may include any conditions relating to active ingredients, labeling indications, warnings and adequate directions for use, prescription or OTC status, and any other conditions necessary and appropriate for the safety and effectiveness of drugs covered by the monograph. § 130.301(a)(5), 37 Fed. Reg. 9474.

The final order provides that after his receipt of the report and recommendations of an advisory review panel, the Commissioner will publish a proposed order containing "a monograph . . . establishing conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded," and permitting written comments. § 130.301(a)(6), 37 Fed. Reg. 9474. After reviewing the comments the Commissioner will publish a tentative final order to which any interested party may file written objections and request "an oral hearing" (*i.e.*, an oral argument) before the Commissioner. § 130.301(a)(7), 37 Fed. Reg. 9474. After reviewing the objections and considering "the arguments made at any oral hearing," the Commissioner will publish "a final order containing a monograph *establishing* conditions under which a category of OTC drugs is generally recognized as safe and effective and not misbranded." (Emphasis added.) § 130.301(a)(9), 37 Fed. Reg. 9475. This latter order is defined as constituting "final agency action from which appeal lies to the courts." § 130.301(a)(10), 37 Fed. Reg. 9475.

C. The Standards To Be Employed

The final order establishes mandatory standards to be employed in determining whether a drug is "safe," "effective," and "generally recognized as safe and effective." Those standards are applicable to both the advisory review

panel and the Commissioner. The final order states, "The advisory review panel, in reviewing the data submitted to it and preparing its conclusions and recommendations, and the Commissioner, in reviewing the conclusions and recommendations of the panel and the published proposed, tentative, and final monographs, shall apply the following standards . . . ." § 130.301(a)(4), 37 Fed. Reg. 9474.

The regulations provide that "Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe . . . ." § 130.301(a)(4)(i), 37 Fed. Reg. 9474. They also prescribe an even more rigorous standard, heretofore applicable only to "new drugs," for proof of effectiveness:

> "Proof of effectiveness shall consist of controlled clinical investigations as defined in § 130.12(a)(5)(ii), unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered." § 130.301(a)(4)(ii), 37 Fed. Reg. 9474.

The proposed regulations also specify that "General recognition of safety [and effectiveness] shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data." § 130.301(a)(4)(i) and (ii), 37 Fed. Reg. 9474.

D. The Intended Legal Effect of Final Monographs

The original proposal as published for comment on January 5, 1972, in paragraphs (b)(1) to (4) asserted directly that the Commissioner's determination, as to whether a drug is generally recognized as safe and effective, or

whether its labeling is false, misleading, or inadequate, would constitute a "substantive rule" which could not be challenged in a subsequent legal action for enforcement of the Act. It specifically stated that "an OTC drug which falls within the category of drugs covered by [a] monograph shall be deemed not to be generally recognized . . . as safe and effective . . . unless it complies with all of the conditions established by that monograph" (§130.301(b)(2), 37 Fed. Reg. 88); that a drug exempt from the new-drug provisions by the 1938 or 1962 "grandfather" clauses "shall be deemed to be misbranded and in violation of Section 502 of the Act, unless it complies with all of the conditions established by that monograph" (§ 130.301(b)(3), 37 Fed. Reg. 88); that "an OTC drug falling within the category of drugs covered by [a] monograph shall, prior to its marketing, either comply with all of the conditions established in that monograph or be the subject of an approved new drug application" (§ 130.301(b)(4), 37 Fed. Reg. 88-89); and that "any such drug which fails to meet one or the other of these two conditions shall be *in violation of the Act* and shall be subject to *summary court procedure* for a determination of illegality" (*Id.*). (Emphasis added).

The Commissioner's discussion of the legal effect of the monographs makes clear that the term "substantive rules" is used as synonymous with "legislative rules," in contrast to "interpretive rules"—i.e., that he intends the final monographs to have the force of law. His final order asserts that "It is . . . within the discretion of the Commissioner, subject to court review, to decide whether the circumstances warrant proceeding to enforce the Act through interpretive guidelines that can be collaterally attacked in enforcement litigation or through substantive rules that are binding upon court appeal." Comments, para. 85, 37 Fed. Reg. 9472.

The Commissioner's final order also asserts that he proposes to use rule-making procedures "to particularize

general statutory standards." Comments, para. 85, 37 Fed. Reg. 9471. This also appears to be a reference to the type of legislative rule-making which is sometimes authorized by Congress. The effect of such rules was concisely described in *Superior Oil Company* v. *Federal Power Commission*, 322 F.2d 601, 614 (9th Cir. 1963), in discussing such legislative rule-making by the FPC:

> "[The order being reviewed] brought about the rule amendment by means of which the Commission determined, for prospective application, that certain kinds of price-changing clauses are contrary to the public interest. The rule amendment thereby accomplished thus gave specificity, in a particular area, to the statutory standard of public interest. Assuming that the Commission had substantive authority to promulgate this amendment . . . , the rule had the same function and effect as if it were a statute proscribing, in the same explicit terms, the described price-changing provisions. So viewed . . . the application in a particular case of the explicit standard stated therein no more entitled persons affected to an evidentiary hearing as to the general merit of the standard than would have been the case if this concreteness had been expressed in the statute itself."

Thus, if they are legislative (or "substantive") rules, the factual determinations made in final monographs would not be subject to challenge in subsequent civil or criminal proceedings for their enforcement, and upon judicial review the court could set aside the agency action only if it was found to be arbitrary and capricious, contrary to constitutional right, in excess of the agency's statutory authority, or taken without observance of the procedures required by law. 5 U.S.C. § 706.

The final order omits paragraphs (b)(1) to (4) relating to the legal status of monographs, and gives the following explanation in Paragraph 91 of the comments:

> "Finally, some comments have noted that paragraph (b) is gratuitous, since it merely states the legal en-

forcement position that the Food and Drug Administration intends to adopt in the event of subsequent regulatory action, and therefore should be deleted. It has been pointed out that there is no comparable statement of legal enforcement position in similar agency regulations. The Commissioner finds this comment persuasive, and accordingly has deleted all of paragraph (b). The parts of former paragraph (b) which related to taking regulatory action on non-conforming products and to new drug applications justifying deviation from a final monograph have been added as new subparagraphs (12) and (13) under paragraph (a). The comments have pointed out that the regulations will be substantially followed by industry. Accordingly, it may become unnecessary to institute a substantial amount of regulatory action to enforce final monographs. Development of a specific enforcement policy can await promulgation of final monographs after which the industry response will be apparent. The Commissioner at that time may adopt whatever enforcement policy is best suited to guarantee full compliance by all OTC drugs with the provisions of the act." 37 Fed. Reg. 9472.

It is not clear what the Commissioner means by "enforcement policy," but his position apparently is that he can issue a final monograph, and decide later whether what he issued was an "interpretive guideline" or a "substantive rule." See Comments, para. 85, 37 Fed. Reg. 9472. Thus, his contention is either that the final monographs will have the force of law, or may be given such force after their issuance at his election.

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, *Petitioners*

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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BRIEF FOR E. R. SQUIBB AND SONS, INC. AS AMICUS CURIAE IN SUPPORT OF RESPONDENT

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-394

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, *Petitioners*

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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BRIEF FOR E. R. SQUIBB AND SONS, INC. AS AMICUS CURIAE, IN SUPPORT OF RESPONDENT

INTEREST OF E. R. SQUIBB AND SONS, INC. AS AMICUS CURIAE

This brief amicus curiae in support of Hynson, Westcott and Dunning, Inc. (HW&D), is submitted by E. R. Squibb and Sons, Inc. (Squibb) pursuant to Rule 42 of the Rules of the Supreme Court of the United States.[1]

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[1] The written consent of petitioners and respondent have been lodged with the Clerk.

Squibb is a New Jersey corporation engaged in the manufacture and sale of pharmaceutical products. Squibb is presently engaged in litigation with the petitioners in a review proceeding involving an essentially identical legal issue to one which this Court may decide in this case (*E. R. Squibb and Sons, Inc.* v. *Secretary of Health, Education, and Welfare et al.*, No. 71-2138, presently pending in the United States Court of Appeals for the Third Circuit). The proceeding in which Squibb is a party was argued on January 19, 1973, at which time the Court of Appeals orally indicated an inclination to withhold its decision until this case is decided by this Court. Since the decision of this Court can be controlling on this issue in its case, Squibb has an interest in these proceedings and is submitting this brief amicus curiae.

This brief is limited to the issue of the validity of the procedures followed by the Food and Drug Administration in denying HW&D a hearing on the revocation of its new drug application for Lutrexin. We take no position as to the merits of the data and information which were submitted by HW&D in support of its request for hearing, or on the jurisdictional questions involved in whether HW&D is entitled to an administrative hearing on the new drug status of its product.

QUESTION PRESENTED

Whether, in an agency-instituted license revocation proceeding required by statute to be "after due notice and opportunity for hearing," the administrative agency may adopt a summary judgment procedure in which the license may be revoked without a hearing, without a finding or an evidentiary showing that there is no substantial issue of fact, and without an eviden-

tiary showing by the Agency on the record that the statutory grounds required for revocation exist. (J.A. 490-491)

STATUTORY PROVISIONS AND REGULATIONS INVOLVED

In addition to the provisions cited in petitioners' brief, the issue argued in this brief involves:

Section 7(c) of the Administrative Procedure Act (APA) (5 U.S.C. § 556(d)) which provides in pertinent part:

> § 556—Hearings; presiding employees; powers and duties; burden of proof; evidence; record as basis of decision.
>
> * * *
>
> (d) Except as otherwise provided by statute, the proponent of a rule or order has the burden of proof. . . . A sanction may not be imposed or rule or order issued except on consideration of the whole record or those parts thereof cited by a party and supported by and in accordance with the reliable, probative, and substantial evidence. A party is entitled to present his case or defense by oral or documentary evidence, to submit rebuttal evidence, and to conduct such cross-examination as may be required for a full and true disclosure of the facts. In rule making or determining claims for money or benefits or applications for initial licenses an agency may, when a party will not be prejudiced thereby, adopt procedures for the submission of all or part of the evidence in written form. . . .

The Fifth Amendment to the Constitution of the United States, which provides in pertinent part as follows:

> "No person shall be . . . deprived of life, liberty, or property without due process of law. . . ."

STATEMENT

On March 22, 1969 (prior to the promulgation of the procedural regulations involved in this proceeding) the Food and Drug Administration (FDA) published a Notice of Opportunity for Hearing on the proposed withdrawal of HW&D's license (new drug application) to market the drug Lutrexin in interstate commerce. (J.A. 12).[2] The notice alleged, as grounds for the withdrawal, in essentially statutory language, "that new information before the Commissioner with respect to such drugs evaluated together with the evidence available to him when the applications were approved shows there is a lack of substantial evidence of effectiveness of the drugs in that there is a lack of substantial evidence that lututrin, a component of [Lutrexin], has the effect or contributes to the effect which [Lutrexin] purport[s] or [is] represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof."

By letter dated April 18, 1969, HW&D requested that a hearing be held on the proposed withdrawal of these licenses. (J.A. 14)

On May 8, 1970, the Food and Drug Administration promulgated new procedural regulations purporting to condition the right to a hearing in license revocation proceedings of this type upon compliance with the requirement that the licensee, as a part of its request for a hearing, set forth a "well organized and full factual analysis of the clinical and other investigational data he is prepared to prove in support of his

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[2] J.A. refers to the Joint Appendix filed by the parties in this case and in Nos. 72-414, 72-528, 72-555, and 72-666, which have been consolidated with this case.

opposition to the notice of opportunity for hearing." According to the new regulations, the "request for hearing may not rest upon mere allegations or denials but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing." In the absence of such a showing the regulations permit the Commissioner to enter an order withdrawing the license without a hearing and without the presentation of any evidence by the Agency, 21 C.F.R. 130.14. (J.A. 490-491)

By letter dated May 19, 1970, eleven days after the promulgation of the new procedural regulations, the Commissioner wrote to HW&D demanding that it amend its request for hearing to comply with this new requirement. (J.A. 20)

HW&D at first refused to amend its request on the ground that the company was entitled to a hearing under the regulations in effect at the time the notice of opportunity for hearing was published. (J.A. 21) Subsequently, on October 16, 1970, HW&D did submit (1) a 4-page listing of data and information which it stated constitutes "substantial evidence," as defined in the May 8, 1970 regulations, thereby requiring that a hearing be held, and (2) seven affidavits (citing 11 studies), and other documents and correspondence in support of both its position that Lutrexin is not a "new drug," and the existence of "substantial evidence" requiring a hearing. (J.A. 24-32)

The Food and Drug Administration did not place into the record any evidence, data, information, affidavits, statements, or analysis of the material presented by HW&D, nor did it attempt to introduce or present any information to show the absence of any genuine

issue of fact in this proceeding. No such showing is required by the 130.14 procedural regulations.

On June 18, 1971, the Commissioner of Food and Drugs published a final order withdrawing approval of HW&D's new drug application for Lutrexin. The request for a hearing was denied "for failure to comply with applicable regulations." The 4-page listing of data and information which HW&D submitted as substantial evidence of effectiveness was dismissed on the grounds that:

> "What the Commissioner is required to do is determine from this material what HW&D may or may not consider relevant and, therefore, relies upon. In the case [of the] bibliographies, the Commissioner would be required to research each article and then determine if it is relevant, or whether HW&D might consider it relevant. Because such a procedure is not contemplated by the regulations, the request for a hearing is denied for failure to comply with applicable regulations." (J.A. 77)

There was no finding by the Commissioner that all of the data submitted or listed failed to show a "substantial issue of a material fact," nor could there have been such a finding since there was no examination of all the data listed.[3]

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[3] The statement from the Order quoted in petitioners' brief, at page 9, to the effect that in any event the material:

> " 'reveals a lack of adequate and well controlled investigations showing that lututrin will have the effect HW&D claims for it . . . ' "

appears to have been taken out of its context in the Order. In the Order, the quoted statement, by its own terms, specifically referred only to that portion of the data which had previously been included

On petition for review, the Court of Appeals held that HW&D is not entitled to a hearing on the issue of whether Lutrexin is a "new drug." This decision was based upon the lack of jurisdiction in the FDA administrative process to decide the issue. That portion of the decision is before the Court in Case No. 72-414.

The Court of Appeals also upheld the validity of the FDA's procedural regulations, but reversed the Commissioner's denial of a hearing on the ground that the data and information presented by HW&D, together with the Commissioner's objections to these data as they appeared in the Order, create "at most" a genuine

---

"in the Lutrexin new drug application . . . ." (J.A. 78) The other listed data cited in support of the existence of substantial evidence, including the additional studies cited (see, J.A. 27-30), was not analyzed or discussed.

The "detailed review of Hynson's documentation" alleged by petitioners' brief at page 9, pertained only to that portion of the data which was cited in the affidavits submitted in support of HW&D claims that its product was not a "new drug." This review appears in the Commissioner's Order under the heading:

> "b. Lutrexin and Trexinest are new drugs within the meaning of 21 U.S.C. 321 (p)(1)." (J.A. 74)

No "detailed review" was presented under the heading:

> "c. The issue of substantial evidence of effectiveness, . . ." (J.A. 77)

with respect to the list of data submitted by HW&D on that issue (J.A. 27-30). To the extent that the data cited in the affidavits submitted to support "not new drug status" was also cited by HW&D in support of the existence of "substantial evidence," the analysis under "b" could, of course, have been utilized by the Commissioner under "c" for that portion of the "substantial evidence data." Even if that were done, however, there was still a substantial listing of data not reviewed "because" according to the Commissioner's Order, "such a procedure is not contemplated by the regulations." (J.A. 77-78)

issue of fact to be resolved at a hearing upon proper evidence. The petitioners in this case seek to have the Commissioner's Order reinstated.

The validity of the procedural regulations has been raised by HW&D as an alternate ground for affirmance, and argued by petitioners in their brief at pages 21-24.

ARGUMENT

I

INTRODUCTION

The Food and Drug Administration's procedural regulations involved in this proceeding (21 CFR 130.14) are, according to that agency, "an adaptation of the summary judgment procedures of the District Courts," 35 F.R. 7250, 7251 (May 8, 1970). Petitioners' brief, page 23, contends that "several other agencies currently have similar rules dispensing with a hearing when there is no genuine issue of fact to be determined."

However, all existing summary judgment procedures, whether administrative or judicial, other than the FDA's, incorporate the requirement that the moving party must show by documentary, admissible evidence that there is no genuine issue as to any material fact. Petitioners' regulations require no such showing by the FDA. Instead, they require the party defending against the "motion" to come forward with an initial, independent presentation of evidence establishing the existence of a genuine issue of fact in order to obtain a hearing. Under its regulations the FDA, by simply alleging in general statutory terms that a license should be revoked, thereby purports to shift the burden of

coming forward with proof both on the summary judgment motion, and on the issue of whether the license may be revoked, to the defending party.

Where, in a case such as this, the FDA decides that a licensee has not even complied with the requirement that evidence be presented,[4] the license may be revoked without the presentation of any evidence by the Commissioner.

It is precisely the absence of those safeguards embodied in both Rule 56 of the Federal Rules of Civil Procedure and the administrative summary decision rules and practices cited by the petitioner, but deliberately omitted from FDA's procedural regulations § 130.14, which cause the latter regulations to be, in the words of the Court of Appeals for the District of Columbia, "fundamentally defective,"[5] and violative of

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[4] The FDA has applied these regulations to deny a hearing in every new drug application license revocation since the promulgation of these regulations. The factual settings of these denials have varied from cases where no data was submitted in support of the request for hearing or analyzed in the final order, e.g., *USV Pharmaceutical Corp.* v. *Secretary of Health, Education and Welfare*, 466 F.2d 455 (C.A.D.C., 1972), where the Commissioner's Order was reversed; and *Ciba Geigy Corp.* v. *Richardson*, 446 F.2d 466 (C.A. 2, 1971), where the Commissioner's Order was upheld; to cases where data was submitted and an analysis of that data was contained in the final order, e.g., *Upjohn Co.* v. *Finch*, 422 F.2d 944 (C.A. 6, 1970), where the Commissioner's Order was upheld; and *E. R. Squibb and Sons, Inc.* v. *Richardson*, No. 71-2138 (C.A. 3), where affidavits were also submitted to establish that the data submitted constitutes "substantial evidence," this case is pending.

[5] *USV Pharmaceutical Corp.* v. *Secretary of Health, Education and Welfare*, 466 F.2d 455 (C.A.D.C. 1972). Although decided on August 14, 1972, before certiorari was allowed in these consolidated cases, the government did not petition this Court for certiorari in that case.

the requirements of the Federal Food, Drug, and Cosmetic Act (the Act), the Administrative Procedure Act (APA), and procedural due process.[6]

II

AS APPLIED IN THIS CASE, PETITIONERS' "SUMMARY JUDGMENT" REGULATION VIOLATES BOTH CONSTITUTIONAL AND STATUTORY REQUIREMENTS

Congressional delegation of quasi-judicial functions to administrative agencies has not relieved those agencies of compliance with fundamental due process requirements. *Ohio Bell Tel. Co.* v. *Public Utilities Commission,* 301 U.S. 292, 304; *Morgan* v. *United States,* 304 U.S. 1, 15-19. *See also, Final Report of the Attorney General's Committee on Administrative Procedures,* Senate Document No. 8, 77th Cong., 1st Sess., p. 62 (1941). In addition, Congress has itself prescribed both general and specific procedural requirements which these administrative agencies must follow in carrying out their limited assigned functions. The petitioners' May 8th hearing regulations, 21 C.F.R. 130.14, on the basis of which HW&D was denied its right to a hearing in this proceeding, as applied in this proceeding, violate both these constitutional and statutory limits.

This is not to say that a hearing would be required on applications where the application or request for a

[6] Even if due process and the Administrative Procedure Act did not require a full fair hearing including the proper allocation of the burden of proof, the Federal Food, Drug, and Cosmetic Act itself requires that an order withdrawing a New Drug Application "shall state the findings on which it is based," § 505(e), 21 U.S.C. 355(e), (J.A. 480) and that on appeal those findings of fact must be "supported by substantial evidence," section 505(h), 21 U.S.C. 355(h) (J.A. 480). The license cannot be withdrawn without any evidentiary showing by the Commissioner.

hearing does not "state a valid basis for a hearing," *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192; *Federal Power Commission* v. *Texaco, Inc.*, 377 U.S. 33. Administrative procedures may include the equivalent of motions under Rule 12 of the Federal Rules of Civil Procedure to dismiss for failure to state legal grounds upon which relief can be granted, or for judgment on the pleadings. This principle is not, however, pertinent to the present case since the Commissioner has not alleged the legal inadequacy of the allegations made by HW&D in its request for a hearing. Rather, he has refused to hold a hearing on the ground that HW&D allegedly failed to comply with the requirements of 21 C.F.R. 130.14 by presenting what the Commissioner will accept as a "well-organized" analysis of adequate supporting evidence showing the existence of a material issue of fact.

Further, Squibb does not contend that the mere allegation of adequate legal grounds must, in all cases, entitle a party to an evidentiary administrative hearing, any more than legally adequate pleadings necessarily entitle a litigant in a District Court to a trial. Administrative agencies should not be expected to waste their time on hearings where it can be shown that there is no genuine or material issue of fact. Unless prohibited by statute, rules for administrative summary judgment, with proper observance of required statutory and constitutional safeguards, may be adopted for this purpose. These principles are not disputed by Squibb in this case.

What is in dispute is whether the procedures followed here have been adequate to meet basic statutory and constitutional requirements.

A. Burden of Proof

Section 7(c) of the APA (5 U.S.C. § 556(d)), which is applicable to these proceedings, provides that "[e]xcept as otherwise provided by statute, the proponent of a rule or order has the burden of proof." Both logic and the legislative history of the APA require that the "burden of proof" be construed to include the "burden of coming forward with a prima facie case." Thus, in discussing the effect of proposed section 7(c), the Senate Report states, "[t]hat the proponent of a rule or order has the burden of proof means . . . that the party initiating the proceeding has the general burden of coming forward with a prima facie case." Sen. Doc. No. 245, 79th Cong., 2d Sess., 208, 270 (1946). In this case, the Commissioner is the party who initiated the proceedings withdrawing approval of HW&D's new drug application and, accordingly, the burden of coming forward with a *prima facie* case rests squarely upon his shoulders.

The allocation of the burden of proof upon the Commissioner is not only required by the clear and unambiguous language of the APA but is well supported by case law. The Courts of Appeals have insisted that where an agency is the proponent of an Order in an adjudicatory proceeding, it cannot require the party who denies the validity or propriety of that Order to show cause why the Order should not be effectuated. See, e.g., *Saltzman* v. *Stromberg Carlson Telephone Manufacturing Co.,* 46 F.2d 612 (C.A.D.C., 1931); *Philadelphia Co.* v. *Securities and Exchange Commission,* 175 F.2d 808 (C.A.D.C., 1948), vacated as moot, 337 U.S. 901.

Despite petitioners' claim that ". . . every Court that has ruled on the question . . . has upheld the lawfulness

of the Commissioner's regulations . . . ," the fact is that the only Court of Appeals which has discussed or analyzed the issues involved in the allocation of the burden of proof under these regulations, has held "the procedures followed by the Commissioner were fundamentally defective." *USV Pharmaceutical Corp.* v. *Secretary of Health, Education, and Welfare,* 466 F.2d 455 (C.A.D.C., 1972). That case, in a proceeding essentially identical to this, held that it is incumbent upon the Commissioner, "before calling upon the [licensee] for additional evidence establishing a right to a hearing, to state facts and reasons showing at least prima facie that the evidence before him raised no material issue of fact which would justify a hearing . . . . Before calling upon the [licensee] to answer, the Commissioner, as the moving party, had an obligation to present at least a *prima facie* case for denial of a hearing." (*USV Pharmaceutical Corp* v. *Secretary of Health, Education, and Welfare, supra,* at p. 461) The court in that case reversed the Commissioner's Order withdrawing USV's license without a hearing.[7]

It is the Commissioner who is the proponent of the "Order" withdrawing approval of the new drug application, and it is HW&D who opposes the Order. It is the Commissioner who, by issuing the "Order" of revocation, has assumed the burden of establishing the propriety of the Order. It is up to him to prove the existence of the statutory criteria for withdrawal of new drug applications. He "may not by accusing put

[7] The cases cited by petitioners (Brief p. 24) do, of course, uphold the suspension of licenses pursuant to these regulations. All, however, preceded the *USV* decision, and none discussed the burden of proof issue which was held to be controlling in that case.

the accused upon proof." *Magnolia Petroleum Co.* v. *National Labor Relations Board,* 112 F.2d 545, 548 (C.A. 5, 1940).

It has long been firmly established that administrative hearings, especially in adjudicatory settings, are required to conform to all "the rudiments of fair play . . . assured to every litigant by [due process] as a minimal requirement, ..." As stated by Justice Cardozo in *Ohio Bell Tel. Co.* v. *Public Utilities Commission,* 301 U.S. 292 at 304:

> "Regulatory commissions have been invested with broad powers within the sphere of duty assigned to them by law. Even in quasi-judicial proceedings their informed and expert judgment exacts and receives a proper deference from courts when it has been reached with due submission to constitutional restraints. *West Ohio Gas Co.* v. *Public Utilities Comm'n* (No. 1), *supra,* p. 70; *West Ohio Gas Co.* v. *Public Utilities Comm'n* (No. 2), 294 U.S. 79; *Los Angeles Gas & Electric Corp.* v. *Railroad Commission,* 289 U.S. 287, 304. Indeed, much that they do within the realm of administrative discretion is exempt from supervision if those restraints have been obeyed. All the more insistent is the need, when power has been bestowed so freely, that the 'inexorable safeguard' (*St. Joseph Stock Yards Co.* v. *United States,* 298 U.S. 38, 72) of a fair and open hearing be maintained in its integrity. *Morgan* v. *United States,* 298 U.S. 468, 480, 481; *Interstate Commerce Comm'n* v. *Louisville & N.R. Co., supra.* The right to such a hearing is one of 'the rudiments of fair play' (*Chicago, M. & St. P. Ry. Co.* v. *Polt,* 232 U.S. 165, 168) assured to every litigant by the Fourteenth Amendment as a minimal requirement. *West Ohio Gas Co.* v. *Public Utilities Comm'n* (No. 1), (No. 2), *supra; Brinkerhoff-Faris Co.* v. *Hill,* 281 U.S. 673, 682. Cf. *Norwegian Nitrogen*

Co. v. *United States, supra.* There can be no compromise on the footing of convenience or expediency, or because of a natural desire to be rid of harassing delay, when that minimal requirement has been neglected or ignored." [8]

This principle has been followed and applied in a long line of cases to assure that litigants in administrative adjudications have adequate notice of the action to be taken and of issues to be tried, *Morgan* v. *United States,* 304 U.S. 1, 15-19; to require confrontation and cross-examination, *Greene* v. *McElroy,* 360 U.S. 474, 496-497, *Willner* v. *Committee on Character,* 373 U.S. 96, 103; to require that litigants be supplied with investigative reports supplied to the agency involved, *Gonzales* v. *United States,* 348 U.S. 407, 413-414, *Arndt* v. *United States,* 222 F.2d 484, 488 (C.A. 5, 1955); to require administrative regulations establishing standards for debarment (from participation in Commodity Credit Corporation contracts), and procedures which will include notice of specific charges, opportunity to present evidence and to cross-examine adverse witnesses, all

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[8] It is significant, in view of the petitioners' references to the burden of holding "hundreds or thousands" of pointless hearings (Brief p. 30, fn. 20, to note that the FDA does not now have any hearing examiners on its staff. The last resigned approximately two years ago. Despite its dire predictions of "hundreds or thousands" of hearings based upon the number of products reviewed by the NAS/NRC over the past five or six years, (Brief p. 19, and p. 22 of petitioners' brief in 72/555) petitioners have failed to suggest the one figure in its files which is pertinent to this problem—the number of hearings actually requested during that time.

We do not believe that the Federal Government cannot provide fair constitutional procedures without chaos. Certainly, the Agency should at least first attempt to handle the "problem" by the adoption of summary judgment procedures which conform to our traditional judicial and administrative concepts of "fair play."

culminating in administrative findings and conclusions based upon the record so made, *Gonzalez, et al.* v. *Freeman, et al.,* 334 F.2d 570 (C.A.D.C., 1964); to assure litigants of an unbiased and nonpartisan trier of fact, *NLRB* v. *Phelps,* 136 F.2d 562, 563 (C.A. 5, 1943); to safeguard "the minimal Constitutional requirement" that an agency must "receive and consider competent and material evidence offered by a party in a proceeding before it," *NLRB* v. *Air Associates,* 121 F.2d 586 (C.A. 2, 1941); and, to require that an agency which proposes to take action must assume the burden of proof in respect to the propriety of its proposed action, *Philadelphia Co.* v. *S.E.C.,* 175 F.2d 808 (C.A.D.C., 1948), vacated as moot, 337 U.S. 901; *Saltzman* v. *Stromberg Carlson Telephone Manufacturing Co.,* 46 F.2d 612 (C.A.D.C., 1931).

> "There are certain criteria of fairness in the hearing process which, in the absence of clear evidence of inapplicability in particular circumstances, should regularly be observed. Before adverse action is to be taken by an agency . . . the individual immediately concerned should be apprised not only of the contemplated action with sufficient precision to permit preparation to resist, but before final action, he should *be apprised of the evidence and contentions brought forward against him so that he may meet them* . . . These may properly be termed the *fundamentals ordinarily requisite to a fair hearing* leading to adverse action against an individual." (Emphasis added). *Final Report of the Attorney General's Committee on Administrative Procedure,* Senate Document No. 8, 77th Cong., 1st Sess., 62 (1941).

Conceptually, the Food and Drug Administration procedures violate these "rudiments of fair play" and

the statutory requirements of the APA, in two distinct ways: the administrative summary decision procedure does not require the FDA to show "the absence of a material issue of fact" in order to revoke the license without a hearing; and this and other cases have shown that as a result of the Commissioner's failure to present any evidence of his own, the orders issued in these cases violate the requirement that the Order be "on consideration of the whole record" and "supported by and in accordance with the reliable probative, and substantial evidence," section 7(c), Administrative Procedure Act, 5 U.S.C. 556(d), see also section 505(h), 21 U.S.C. 355(h). (J.A. 480)

(1) Commissioner's summary judgment procedure: failure to show absence of genuine issue of fact

The procedure followed by the Commissioner under his regulations appears to adopt the astonishing presumption that there is "no genuine and substantial issue of fact which precludes . . . the withdrawal of approval of the applications." For, if the request for a hearing by the holder of the license is deemed insufficient to establish such an issue, no hearing will be held. No showing need ever be made by the Commissioner to support his Order denying the hearing. In the present case, the state of the record is such that the Commissioner's denial of a hearing is based upon the allegation that HW&D "has not attempted compliance with [the procedural regulations]," (J.A. 77-78) and therefore has not carried his burden of establishing the existence of a factual issue. The Commissioner has not provided or attempted to provide evidence to affirmatively show the absence of a material issue of fact.

This distinction is, of course, basic to any fair adoption of a summary judgment procedure. A plaintiff is not entitled to summary judgment on the basis of a finding that the defendant has not shown the existence of a substantial issue of fact.

A fundamental principle on motion for summary judgment is that "the moving party . . . has the burden of showing the absence of a genuine issue as to any material fact" and that he is entitled to judgment as a matter of law, even though his opponent may have the burden of proving the facts at trial, *Adickes* v. *S. H. Kress and Co.,* 398 U.S. 144, 157.

Thus, it is Squibb's position that the Commissioner may not enter summary judgment in his own favor unless he first identifies and presents probative evidence of record sufficient to establish the absence of any such factual issues. He cannot merely rely upon a finding that the respondent has not affirmatively shown the existence of such an issue.

The Administrative Conference of the United States has, as indicated in petitioners' brief (P. Br. 23), suggested the adoption of a "Summary Decision Rule," by administrative agencies.[9] This proposed rule, however, provides for motions which may be granted if, but only if, the motion is supported by "pleadings, affidavits, material obtained by discovery or otherwise, or matters officially noticed" which show that there is no genuine issue as to any material fact. The burden is on the moving party to show the absence of any factual issues. If, but only if, such a motion "is made

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[9] 38 U.S.L. Week, 2658, June 9, 1970.

and supported as provided in this rule,"[10] the party opposing the motion is required to respond to establish a genuine issue of fact. By way of answer to the objection that summary judgment rules are not applicable to administrative hearings because "[t]he right to be heard means, at the least, the right of a party to present evidence and to test that offered by his adversary," the draftsmen of this model rule state:[11]

> "The short yet complete answer to these protests is that summary judgment is granted only when the papers filed with the motion clearly reveal that an evidentiary hearing would serve no useful purpose. Summary judgment honors the right to be heard by allowing the party opposing the motion to show the necessity for a trial *and by placing the burden on the party seeking summary disposition.*" (Emphasis supplied).

The petitioners' "summary judgment procedure" as applied in this case places no burden on the agency

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[10] It is not Squibb's contention that a prima facie case must include a showing by the Commissioner that the challenged drugs are ineffective or unsafe. Rather, it is Squibb's position that according to the explicit terms of § 505(e) of the Act the Commissioner must establish that the statutory criteria justifying revocation have been satisfied; i.e., he must come forward, identify and present probative evidence, including "new information" which "with the information available to him when the application was approved" establishes that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have . . . ." (J.A. 479).

[11] E. Gellhorn and W. F. Robinson, *Summary Judgment in Administrative Adjudication*, 84 Harv. L. Rev. 612, 616 (1971).

The proposed "Rule," set out in full in the cited article at page 628, is essentially identical to that which has been adopted by the F.T.C., 16 C.F.R. 3.24, (also cited by petitioners at p. 23 of their brief.)

when seeking summary disposition, but instead shifts the burden of coming forward with proof to the party opposing the motion, and provides for the granting of such an order against that party solely because he has failed to establish the existence of a factual issue. Such an Order, in a license revocation proceeding, clearly violates the APA, section 7(c), 5 U.S.C. § 556(d), due process requirements, and the requirements of the Federal Food, Drug, and Cosmetic Act that the license revocation must be based upon findings of fact and supported by substantial evidence. (§ 505(e) and (h), 21 U.S.C. 355(e) and (h)).

Petitioners appear to speak to this point in footnote 22, on page 32 of their brief, where in discussing *USV v. Secretary of Health, Education, and Welfare,* 466 F.2d 455 (C.A.D.C., 1972) it is contended that the Commissioner may, "by adopting the findings of the NAS/NRC panels rightly place upon the holder of NDA's issued prior to October 10, 1962 (when it was not necessary to submit any proof of effectiveness to receive approval of an NDA) the burden of coming forward with substantial evidence of effectiveness, to avoid withdraw of the approval of that NDA." The short answer to this *post hoc* argument by counsel in this Court is that the Notice of Opportunity for a Hearing in this case (J.A. 12) did not purport to adopt the NAS/NRC findings nor were they even referred to in the "Findings" made in support of the Order.[12] (J.A. 72-78). They did not because the 130.14 regulations under which the Order was issued are not designed for, or limited to, pre-1962 drugs or to situations where

[12] Nor, despite the quoted footnote, did the Commissioner "adopt" or even refer to the NAS/NRC review in the Notice, 33 F.R. 9908 (July 10, 1968), or in the Order, 35 F.R. 16332 (October 17, 1970), involved in the USV case.

NAS/NRC panels have spoken. The regulations provide for the same shift of the burden of coming forward with proof regardless of the vintage of the drug or the grounds alleged for withdrawal.[13] The NAS/NRC Panel review did not constitute any part of the Commissioner's "summary judgment" procedure under 21 C.F.R. 130.14, in this or any other proceeding.[14]

Petitioners' argument is therefore both *post hoc* and purely hypothetical, i.e., *had* the Commissioner adopted the findings of the NAS/NRC Panels, *then* he could have shifted the burden of coming forward with proof. Clearly the Order in this case was not based upon the panel reports because the Commissioner intended to

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[13] In addition to the grounds alleged in this proceeding, i.e.,— "new information . . . that there is a lack of substantial evidence . . ." of effectiveness, 21 U.S.C. 355(e) provides that a new drug application may be withdrawn if, e.g.,—

(1) the drug is "unsafe"

(2) new evidence shows that such drug is not shown to be safe

(3) the application contains any untrue statement of material fact

(4) the applicant fails to maintain certain records or make required reports

(5) on the basis of new information the labeling is false or misleading in any particular. (J.A. 479-480)

[14] The claim that the Notice had "adopted" the NAS/NRC findings was not briefed by either party in the Court of Appeals.

FDA has, in fact, applied these regulations in Notices of Opportunity for Hearing on Proposed Withdrawals of New Drug Applications involving only issues of "safety," and where there was no NAS/NRC, or any other committee opinion available to rely upon, see e.g., Notice of Opportunity for Hearing; Dienestrol Diacetate, 38 F.R. 3211 (February 2, 1973).

In other proceedings, the FDA has applied these regulations where the Order itself admits that the NAS/NRC conclusions were "unclear." Notice Withdrawing Approval of New Drug Applications, 36 F.R. 20543, 20545 (October 23, 1971).

base this Order (like the other Orders where there was no NAS/NRC review available) upon the far broader base of the procedural regulations which purport to automatically shift the burden of coming forward, with no showing of any kind.[15]

(2) Commissioner's final order; failure to present adequately supported findings

The Commissioner's final order in this proceeding must "state the findings on which it is based," 21 U.S.C. 355(e), and be "supported by and be in accordance with the reliable, probative and substantial evidence." 5 U.S.C. 556(d). The "burden of proof" of presenting sufficient probative evidence to support an order must be carried by the Commissioner and the findings must be based upon such evidence. However, under the procedures established by 130.14, no such showing or findings are required, nor were they made in this case.[16]

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[15] If the Court were to consider the argument that the Commissioner had inferentially attempted to adopt the NAS/NRC review as a basis for "shifting the burden of coming forward" we would be faced with the issues of (1) whether HW&D had proper notice of what arguments it was expected to meet on such a "summary judgment" motion, and (2) whether the unsworn, brief summary of views of a committee, which had, according to the summary itself, considered only two published papers (J.A. 7-10), would be sufficient to support a summary judgment decision. ("On summary judgment the inferences to be drawn from the underlying facts contained in such material must be viewed in the light most favorable to the party opposing the motion." *United States* v. *Diebold, Inc.*, 396 U.S. 654, 655.) However, since the Order does not purport to rely upon the Panel reports (nor did the petitioners' brief make this argument in the court below), this issue is not before this Court.

[16] This case was not unique in omitting findings of fact adequate to support either a summary administrative decision or the final order. Among the reported cases, no such findings were made in the orders rendered in *Ciba-Geigy Corp* v. *Richardson*, 446 F.2d 466 (C.A. 2, 1971), 35 F.R. 15253 (Sept. 30, 1970) or *USV Pharmaceutical Corp.* v. *Secretary of Health, Education, and Welfare*, 466 F.2d 455 (C.A.D.C., 1972), 35 F.R. 16332 (Oct. 17, 1970).

That part of the order which dealt with the alleged existence of "substantial evidence" was not and did not purport to be based upon an examination of all the data presented. Rather, the Order specifically recites the Commissioner's refusal to do so because according to the Commissioner, the "materials [relied upon by HW&D] are described for the most part in general terms (e.g., data presented in connection with the New Drug Application for Lutrexin tablets * * * Lutrexin bibliography * * * Trexinest bibliography * * * reprints and abstracts * * *)." The Commissioner specifically refused to "research each article and then determine if it is relevant . . . [b]ecause such a procedure is not contemplated by the regulations . . . ." (J.A. 77-78). Eleven studies were analyzed for the purpose of showing that "Lutrexin [is a] new drug within the meaning of 21 US.C. 321(p)(1)," (J.A. 74-77) and conclusionary general comments concerning what the Commissioner characterized only as "the most basic material in the Lutrexin new-drug application" were presented. (J.A. 78). It is, however, clear, and the Order does not allege otherwise, that these two categories do not exhaust the listing of information and data presented by HW&D in support of its position regarding the existence of "substantial evidence." [17]

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[17] Since this brief is limited to legal procedural issues, we have not attempted to argue whether the findings which were actually made concerning the eleven studies are in fact supported by the record. However, it is apparent that at least certain of the Commissioner's alleged reasons for dismissing these eleven studies were based upon evidence and information which is not in, or supported by, the record. For instance, the Commissioner's criticism (J.A. 75) of the statistical treatment of the Magewski study, "Statistical Evaluation of the Reduction of the Incidence of Prematurity (1968)" criticizes the manner in which the author presented his data concerning "24 [women] with one previous pregnancy" and suggests an alternative presentation. The author's presentation

The absence of adequate findings of fact "on consideration of the whole record" and "supported by and in accordance with reliable, probative, and substantial evidence," to support the Commissioner's conclusions, in statutory language "that on the basis of new information before him with respect to [Lutrexin] evaluated together with the evidence available to him when [such] application was approved, there is a lack of substantial evidence that [it] will have the effects it is purported to have . . ." violates section 7(c) of the Administrative Procedure Act, 5 U.S.C. 556(d), and the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355(e) and (h), see *Universal Camera Corp.* v. *NLRB*, 340 U.S. 474, *Labor Board* v. *Brown*, 380 U.S. 278, 291.

CONCLUSION

The Court of Appeals in this case upheld the validity of the Commissioner's regulations but reversed the order withdrawing the new drug application without a hearing on the ground that "the showing of [HW&D] was such that under a reasonable construction of the Commissioner's own regulations, as well as under

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(J.A. 110) appears to be for the purpose of evaluating the effectiveness of Lutrexin for increasing the likelihood of "live births" by these 24 women, as compared with their own prior experiences during their own prior pregnancies. The Commissioner's suggested alternative "paring" would result in a comparison of the "live birth" percentage in these 24 women during their second pregnancies, against the "live birth" percentage in 15 other women during their first and second pregnancies. Which of these comparisons is more meaningful is, at the very least, a question of fact requiring evidentiary support. Similarly, although the author analyzed the data in the same Table I by the "chi-square method," the Commissioner states that it "does not admit to a statistical evaluation by the chi-square method since the test is based on the assumption that each number of the columns in Table I is the sum of independent yes or no responses . . . ." (J.A. 75) Such a finding also requires, at the very least, a factual basis in expert testimony, subject to cross-examination and rebuttal by HW&D.

familiar principles of due process and the requirements of the Administrative Procedure Act, it was entitled to an impartial hearing before its NDA was withdrawn." (J.A. 179)

The petitioners have, in this case, sought review of that finding. Squibb recognizes that this Court may affirm the decision of the Court below for the reasons stated by the Court of Appeals—i.e., Hynson, Westcott and Dunning's showing was adequate to require a hearing even under the Commissioner's regulations—without the need to reach the question of whether the regulations are themselves valid. Indeed, this course may be preferable since the adequacy of that showing was the ground relied upon in the Court of Appeals. If this is done, however, the fact that the validity of the regulations has not been decided by this Court should be clearly stated so that the important questions of administrative law presented by these regulations, and potentially affecting administrative practices by all agencies, will not be foreclosed without adequate consideration by this Court.

On the other hand, if the Court should find that HW&D's showing was not adequate under the Commissioner's regulations, it must of necessity reach the issue of the validity of these regulations. On this issue, we submit that these regulations are invalid, and that the judgment of the Court of Appeals should be affirmed on that ground.

Respectfully submitted,

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-394

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS, PETITIONERS

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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MEMORANDUM FOR USV PHARMACEUTICAL CORPORATION, AMICUS CURIAE

USV Pharmaceutical Corporation is the petitioner in No. 72-666 (*USV Pharmaceutical Corp.* v. *Weinberger*), one of the cases before this Court arising under the Federal Food, Drug, and Cosmetic Act of 1938[1] with which the instant

[1] 52 Stat. 1040, *as amended*, 21 U.S.C. §§ 301 *et seq.*

case has been consolidated.[2] The purpose of this memorandum is to bring to the Court's attention the relationship between the instant case and an administrative proceeding to which USV is a party, related to the proceedings involved in No. 72-666, and which is now pending before the Commissioner of Food and Drugs.[3]

1. The USV administrative proceeding to which we refer, like the instant case, arises under Section 505(e) of the Act.[4] It was initiated by the Commissioner's publication of a proposal to revoke approval of the new drug applications held by USV for some of the products involved in the declaratory judgment proceedings before this Court in No. 72-666.[5] A final order of revocation, entered by the Commissioner without a hearing on the ground that USV had not attempted affirmatively to establish the existence of a material factual issue requiring a hearing, was set aside by the Court of Appeals for the District of Columbia Circuit for failure to conform to the requirements of administrative due process."[6] The government decided not to

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[2] 409 U.S. — (1973). The other three cases are *Hynson, Westcott & Dunning, Inc.* v. *Weinberger*, No. 72-414, *CIBA Corp.* v. *Weinberger*, No. 72-528, and *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72-555.

[3] *Drugs for Human Use Containing Rutin et al.*, Dkt. No. FDC-D-112 (FDA).

[4] 52 Stat. 1053, *as amended*, 21 U.S.C. § 355(e).

[5] The initiation of the administrative proceeding precipitated the commencement of the declaratory judgment action by USV.

[6] *USV Pharmaceutical Corp.* v. *Secretary of HEW*, 466 F.2d 455, 462 (D.C. Cir. 1972). To avoid confusion with the decision of the Court of Appeals for the Fourth Circuit in No. 72-666, the D.C. Circuit decision will hereafter be cited as "*USV II*". That opinion is reproduced in the appendix to the petition for certiorari in No. 72-666 (pp. 36a-49a).

petition for certiorari to review the decision,[7] and the matter is again before the Commissioner pursuant to the judgment of the court of appeals remanding for further proceedings.[8]

The issue principally discussed in the opinion of the D.C. Circuit was the Commissioner's misapplication of summary judgment principles so as to require USV, the respondent in the revocation proceeding, to justify in the first instance its request for a hearing on the Commissioner's bare-bones proposal to revoke approval of its new drug applications.[9] The Court recognized that a summary judgment procedure may be used in Section 505(e) proceedings "in appropriate circumstances", but ruled that the provision in that statute giving an NDA holder "opportunity for hearing" before approval of his NDA is revoked "does restrict the application of that procedure to cases in which no material factual issue is presented and a hearing would be a hollow formality."[10] In deciding whether a material factual issue was presented with respect to the proposed revocation of approval of USV's new drug applications, the court of appeals continued, the Commissioner "was not an impartial arbiter of the contentions of opposing parties, but was himself the moving party undertaking to support his own pro-

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[7] Resp. Mem. on Petition for Certiorari, p. 4 n. 6, *USV Pharmaceutical Corp.* v. *Weinberger*, No. 72-666.

[8] The Commissioner has *sua sponte* stayed the proceedings before him pending the decision of this Court in No. 72-666 (letter dated October 17, 1972, from HEW Ass't Gen. Counsel Hutt to counsel for USV).

[9] The two remaining errors were the absence of adequate findings and conclusions to support the final order (466 F.2d at 461-62), and the Commissioner's arbitrary and unexplained failure to give USV "an opportunity to submit additional evidence or plead over when its request for a stay [pending disposition of the declaratory judgment proceedings in the district court] was denied" (*id.* at 462.)

[10] *Id.* at 460 n.5.

posed order." [11] Moreover, the statutory basis for revocation of approval was observed to be "new information, together with the evidence available when approval was originally granted." [12]

The court held that certain "limited steps" would therefore be "basic to administrative fairness":[13]

> "In this situation • • • it was incumbent upon the Commissioner, before calling upon the petitioner for additional evidence establishing a right to a hearing, to state facts and reasons showing at least prima facie that the evidence before him raised no material issue of fact which would justify a hearing. • • • Before calling upon the petitioner to answer, the Commissioner, as the moving party, had an obligation to present at least a prima facie case for denial of a hearing. [Citations omitted.] Only after such a presentation could the Commissioner fairly impose upon petitioner the heavy sanctions of 21 C.F.R. § 130.14." [14]

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[11] *Id.* at 461.

[12] *Ibid.*

[13] *Ibid.*

[14] *Ibid.* The court buttressed its conclusion that "administrative fairness" so requires by referring to the well-established doctrine under Rule 56 of the Federal Rules of Civil Procedure that a party moving for summary judgment "may not, by the bare assertion that he is entitled to summary judgment, shift to his opponent the burden of establishing the contrary" (*ibid.*). Also cited were this Court's decisions in *Greene* v. *McElroy*, 360 U.S. 474, 496 (1959) that one of the "principles • • • relatively immutable in our jurisprudence • • • is that where governmental action seriously injures an individual, and the reasonableness of the action depends on fact findings, the evidence used to prove the Government's case must be disclosed to the individual so that he has an opportunity to show that it is untrue", and in *Southern R. Co.* v. *Virginia*, 290 U.S. 190, 197 (1933) that "an administrative officer may [not] be empowered, without notice or hearing, to act with finality upon his own opinion and ordain the taking of private property."

In the USV proceeding, the D.C. Circuit found, no such prima facie case for denial of a hearing had been presented by the Commissioner, and a final revocation order consequently could not be entered without a hearing merely because USV had not attempted to demonstrate the existence of a material factual issue justifying a hearing. Both the Commissioner's notice of intent to initiate a proceeding [15] and the subsequent notice of opportunity for hearing [16] merely "parroted the language of the statute without reference to any evidence." [17] Although the original notice of intent referred to reports of expert panels rendered in the NAS-NRC Drug Efficacy Study,[18] these reports "were cryptic and conclusory, without any statement of supporting facts." [19] The final order revoking approval of USV's new drug applications was accordingly set aside,[20] because, *inter alia*, "such an application of the Commissioner's summary judgment rule is not in harmony with the principle of the rule and is fundamentally unsound and unfair." [21]

2. Throughout its brief in the instant case the government appears to assume that, contrary to the decision of the D.C. Circuit in *USV II*, respondent Hynson was *obligated* to come forward with evidence in response to the Commissioner's bare-bones notice of opportunity for hearing (A.

[15] A. 290-91. ("A. —" refers to the Joint Appendix in the instant case and those, including No. 72-666, with which it has been consolidated.)

[16] A. 293-97.

[17] 466 F.2d at 461.

[18] The nature and function of these panels is described at pp. 16-17 of the Brief for Petitioners in No. 72-555, *Weinberger* v. *Bentex Pharmaceuticals, Inc.*

[19] 466 F.2d at 461. The reports were reproduced in full earlier in the court's opinion (*id.* at 458).

[20] *Id.* at 462.

[21] *Id.* at 461.

12-14) if it wished to avoid entry of a final order of revocation without any hearing. The correctness of that assumption, however, does not seem to be in issue in this case, since, unlike USV, Hynson—whether obligated or not—did in fact come forward with such evidence.[22]

Thus, this case does not tender—as would the D.C. Circuit's *USV II* decision had the government brought it here for review—the question of which party, the Commissioner or the respondent, has the *initial* burden of coming forward with a showing on the existence or non-existence of a factual issue requiring a hearing. It is our understanding that respondent Hynson will rely upon the *USV II* decision as an alternative ground for affirmance of the judgment below. We would stress, however, the substantial difference described above between the posture of the instant case and that of the USV administrative proceeding when the Commissioner's final revocation orders were respectively entered. In the light of this difference, a decision by the Court that the Commissioner was entitled to enter a final revocation order against Hynson without a hearing in the circumstances of this case could not be taken as *sub silentio* overturning or undermining the ruling in *USV II*, or questioning the applicability to Section 505(e) revocation proceedings of the general principles of constitutional and administrative law on which the D.C. Circuit relied.

This memorandum is therefore filed out of an abundance of caution in order to safeguard USV's interests, in the event of a decision adverse to Hynson, by making explicit

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[22] Nor does the government appear to view the correctness of its assumption as properly before this Court for decision. The point is not specifically argued in the government's brief, and, indeed, the only explicit reference to it is the single observation (Pet. Br. 22), offered without explanation or justification, that the Commissioner's summary judgment regulation "does no more than place upon the party demanding a hearing the responsibility to present 'the evidence needed to make out a *prima facie* case.' "

at this time the distinction between the instant case and *USV II*, where the decision in USV's favor has become final by operation of law as a consequence of the governments's determination not to seek certiorari.

Respectfully submitted,

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April 4, 1973

APR 4 1973

In The

Supreme Court of the United States

October Term, 1972

No. 72-251

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

On Writ of Certiorari to the United States Court Of Appeals for the Fourth Circuit

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-394

CASPAR W. WEINBERGER, Secretary of Health, Education and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs,

Petitioners

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

On Writ of Certiorari to the United States Court Of Appeals for the Fourth Circuit

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BRIEF FOR RESPONDENT HYNSON, WESTCOTT AND DUNNING, INCORPORATED

OPINIONS BELOW

The opinion of the court of appeals (J.A. 173-180)[1] is reported at 461 F.2d 215. The order of the Commissioner of Food and Drugs was published in the Federal Register on June 18, 1971 (J.A. 72-78; 36 Fed. Reg. 11763).

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[1] "J.A." refers to the Joint Appendix filed by the parties in this case and in Nos. 72-414, 72-528, 72-555, and 72-666, with which this case has been consolidated.

JURISDICTION

The judgment of the court of appeals (J.A. 181) was entered on May 24, 1972. The petition for a writ of certiorari was filed, pursuant to an extension of time granted by Mr. Justice Rehnquist, on September 7, 1972. On January 8, 1973, this Court granted the petition and consolidated the case with four other cases in which it also granted petitions for a writ of certiorari. The jurisdiction of this Court rests on 28 U.S.C. 1254(1) and 21 U.S.C. 355(h).

STATUTORY PROVISIONS AND REGULATIONS INVOLVED

Section 505(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(c); J.A. 477-478) provides in pertinent part:

Within one hundred and eighty days after the filing of [a new drug] application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be

issued within ninety days after the date fixed by the Secretary for filing final briefs.

Section 505(e) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(e); J.A. 479) provides in part:

> "The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds * * * (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling thereof * * *."

21 Code of Federal Regulations, Part 130

(Revised as of January 1, 1969)

[In effect when Hynson, Westcott & Dunning, Incorporated, accepted an opportunity for a hearing before FDA on April 18, 1969]

Section 130.14 Contents of notice of hearing.

(a) The notice to the applicant of opportunity for a hearing on a proposal by the Commissioner to refuse to approve an application or to withdraw the approval of an application will specify the grounds upon which he proposes to issue his order. On request of the applicant, the Commissioner will explain the reasons for his action. The notice of hearing will be published in the FEDERAL REGISTER and will specify that the applicant has 30 days after issuance of the notice within which he is required to file a written appearance electing whether:

(1) To avail himself of the opportunity for a hearing at the place specified in the notice of hearing; or

(2) Not to avail himself of the opportunity for a hearing.

(b) If the applicant elects to accept the opportunity for a hearing by written request within 30 days after such notice, a hearing examiner will be named and he shall issue a written notice of the time and place at which the hearing shall commence, not more than 90 days after the expiration of such 30 days unless the hearing examiner and the applicant otherwise agree.

(c) The hearing will be open to the public: *Provided, however*, That if the Commissioner finds that portions of the application which serve as a basis for the hearing contain information concerning a method or process which as a trade secret is entitled to protection, the part of the hearing that involves such portions will not be public unless the respondent so specifies in his appearance.

[28 F.R. 6377, June 20, 1963, as amended at 29 F.R. 7020, May 28, 1964]

QUESTIONS PRESENTED

1. Whether, despite the evidence submitted by Hynson, Westcott and Dunning, Incorporated, the Commissioner of Food and Drugs may, without a hearing, make a determination that there is a lack of substantial evidence of effectiveness of the drug Lutrexin, within the meaning of the Federal Food, Drug and Cosmetic Act (as amended by the Drug Amendments of 1962) and the Commissioner's regulations and, upon the basis of such determination, withdraw approval of the new drug application for such drug.

2. Whether the regulations under which a hearing was denied are valid.

3. Whether Hynson, Westcott & Dunning was entitled to a hearing by virtue of its timely acceptance of the

proffered opportunity for a hearing under regulations then in effect, regardless of its rights under the regulations thereafter adopted under which a hearing was denied.

SUMMARY OF ARGUMENT

1. In Point I we analyze the affidavits and medical studies submitted by respondent Hynson, Westcott and Dunning, Incorporated (HW&D) to FDA, showing that they raise an issue of material fact as to the effectiveness of Lutrexin. The affidavits and studies and the Commissioner's analysis of them in his order (J.A. 72) show the existence of disputed issues of fact as to whether the medical data contains adequate and well-controlled studies.

2. FDA's so-called "summary judgment" regulations bear little resemblance to the summary judgment requirements of Rule 56 to which the agency has likened them. They are unfair on their face since, unlike the Rule 56 procedures, they permit an *ex parte* decision by the movant (FDA) without the submission of any evidence to support its position, and give the manufacturer no opportunity to show that the medical studies submitted raise a substantial issue of material fact requiring a hearing. Nor do the regulations provide for an impartial decision-maker to pass on the summary judgment question.

The Court of Appeals in the instant case and the Court of Appeals for the District of Columbia Circuit have pointed out these deficiencies in the regulations.

The Commissioner acts as both prosecutor and judge of the validity of his actions. It cannot accurately be said, as the Government does, that the summary judgment procedures of the Federal Trade Commission and the National Labor Relations Board are "similar" to

those of FDA, since those agencies provide for an impartial decision-maker to decide motions for summary judgment.

It is clear from the decisions of this Court that the party moving for summary judgment has the burden of showing the absence of a genuine issue of material fact —a burden which FDA has shifted to the holder of an NDA under its regulations.

The issue in the instant case is one of fact—whether there is substantial evidence of the efficacy of Lutrexin. Under the decisions of this Court, due process requires an opportunity to confront and cross-examine witnesses —a trial-type hearing.

3. The analysis in Point I, *infra*, of the affidavits shows that the affidavits and medical literature submitted by HW&D raise a factual issue which is genuine and substantial and requires a hearing on the question of the existence of substantial evidence of effectiveness of Lutrexin.[2]

It is no answer to say, as the Government does, that FDA would be swamped with hearings beyond its capacity to cope, if a hearing were required in a case such as the instant one. The law as declared by the courts is that such difficulties do not excuse compliance with the statute or requirements of due process.

Moreover, the Government has made no showing that, in fact, FDA would be swamped by hearings, which would be limited to cases in which there was an issue of material fact as to the existence of substantial evidence of effectiveness. Each case must be decided on its merits and it seems evident that the Government is not in a position to accurately predict, or even estimate, the

[2] In our brief in No. 72-414 (Point II) we maintain that a hearing is also required on the jurisdictional questions arising under the Act as amended in 1962.

number of situations in which a hearing would be required.

The Government states that HW&D need make only a *prima facie* showing of the existence of substantial evidence; but then it proceeds to equate such a showing with an actual showing of substantial evidence. This was not the intent of Congress as the language of the statute and its legislative history demonstrate. On the contrary, the statute and its history show that the burden of proof in withdrawal-of-approval proceedings under Section 505(e)(3) is upon FDA itself. This is evident from a comparison of the provisions of Section 505 (b) and (d) (which place the burden of coming forward with convincing evidence of safety and effectiveness upon an *applicant* for an NDA), with the withdrawal provisions of Section 505(e).

4. We show, in Point IV, that HW&D was vested with the right to a hearing under the regulations in effect when HW&D accepted FDA's offer of a hearing and that this view is supported by the decisions of this Court. FDA failed to follow its own rules in such a case as this one. The substitution of the new regulations of May 8, 1970 cannot be made a basis for denying a hearing (even if HW&D were not entitled to a hearing under the new rules), under the holding of this Court in *Greene* v. *United States*, 376 U.S. 149 (1964) and the holding of the Sixth Circuit in *Upjohn* v. *Pennsylvania Railroad Company*, 381 F.2d 4 (1967).

ARGUMENT

The Government's Statement of the Question Presented

The Government's statement of the Question Presented is inaccurate. It assumes that HW&D has not submitted to the Commissioner "substantial evidence" of the effectiveness of Lutrexin and has therefore not complied with

the Commissioner's regulations of May 8, 1970 relating to hearings in a proceeding to withdraw approval of a new drug application (NDA).[3] One of the basic questions in this case is whether the evidence submitted by HW&D is "substantial" within the meaning of the statute and the Commissioner's regulations. For this reason we have rephrased the Question Presented as stated in the Government's brief (p. 2), and numbered it 1.

HW&D stated in its brief in opposition to the Government's petition for a writ of certiorari (p. 3) that, if the petition should be granted respondent would want to place two additional question before this Court which were argued in the Court below.

Accordingly, we have added two questions (numbers 2 and 3), as stated in our Memorandum in Opposition to the Government's petition for certiorari.

In its brief the Government expresses doubt whether the issues raised in numbers 2 and 3 of the Questions Presented are properly before this Court. It then proceeds to argue the merits of those issues (Br. 21; footnote 17, p. 24).

It is submitted that both questions 2 and 3 are "fairly comprised" within the basic question (No. 1) of whether HW&D is entitled to a hearing, within the meaning of the second sentence of this court's rule No. 40(d)(1). If, as we maintain, the statute requires a hearing in the instant case, it seems obvious that the validity of the Commissioner's hearing regulations of May 8, 1970 is called into question, even by the Question Presented as stated in the Government's brief. That Question, even as phrased by the Government, seems clearly to comprehend the question of whether due process requires a hearing in this case, regardless of whether the right to

[3] The regulations, as amended, appear at 21 CFR 130.12(a)(5) and 21 CFR 130.14 (J.A. 487-491).

the hearing arises under the statute, under the May 8, 1970 regulations, or under the regulations in effect when HW&D first requested a hearing.

Background

The Government notes that HW&D requested a hearing on April 18, 1969 and states that "Before the hearing could take place" the company, on August 19, 1969, filed suit in the United States District Court for the District of Maryland, seeking declaratory and injunctive relief from withdrawal of "approval" of the NDA for Lutrexin by FDA (Br. 6).

We are not certain of the reasons for this implication that a hearing would have been held had HW&D not filed the action in Baltimore.[4] It serves to recall, however, the fact that in its memorandum in support of its motion to dismiss in the Maryland case FDA *repeatedly* stressed that Congress intended that HW&D should have a hearing and that FDA was obligated to hold the hearing. For example, the Memorandum stated (p. 19):

> "Section 505 provides that an opportunity for a hearing be extended to an applicant before an approved NDA is revoked. When, as in the instant case, the applicant elects to proceed to hearing, *revocation of the NDA can be effected only after the Commissioner has, on the basis of the hearing record made certain statutory findings of fact. No alternate procedure for revocation is authorized by the Act.* (Emphasis supplied)."

That memorandum was filed in the latter part of October, 1969, *after* the first promulgation on September 19, 1969 of the regulations which defined "adequate and

[4] The rules then in effect required that the hearing commence within 90 days after acceptance of the opportunity to be heard unless the hearing examiner and the applicant otherwise agreed (21 CFR 130.14(b), revised as of January 1, 1969).

well-controlled" studies and established the criteria which must be met to obtain a hearing.[5] Thus, even after the regulations had been published, FDA was of the opinion that it was required to give HW&D a hearing. This had been the view of both industry and FDA since the enactment of Section 505. This view had not been changed by the 1962 Amendments to Section 505. Thus, in *In the Matter of Serc Tablets (Unimed, Inc.)*, Docket No. FDC-D-111 (1969), an NDA withdrawal proceeding in which FDA granted a hearing, the Government, by its attorneys, unequivocally recognized the right to a hearing and stated in a memorandum submitted to the hearing examiner some three months after HW&D had accepted its opportunity for a hearing:

> "When, as in the instant case, the applicant elects to proceed to a hearing, revocation of the NDA can be effected only after the Commissioner has on the basis of the hearing record made certain statutory findings of fact. *No alternate procedure for revocation is authorized by the Act* (Memorandum in Opposition to Respondent Unimed's Motion to Suspend the Hearing, pp. 8-10, emphasis supplied)."

These facts lend emphasis to the view that the real reason for the agency's present stance is the desire not to hold hearings because of the alleged multiplicity of hearings which might be required under the Act. This, in fact, is a principal argument of the Government and is discussed in Point IIIA of our argument, *infra*.

The report of the NAS-NRC Panel on Drugs Used in Disturbances of the Reproductive System stated that

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[5] The September 19, 1969 regulations were set aside because FDA failed to follow the procedural scheme of the statute. *Pharmaceutical Manufacturers Association* v. *Finch*, 307 F. Supp. 858 (D. Del. 1970). The present regulations of May 8, 1970 (J.A. 487-491) are the same as the September 19, 1969 regulations, insofar as here relevant.

Lutrexin was "possibly effective" for each claim made for the drug; that, in the case of the claim of effectiveness for dysmenorrhea, sound documentation was not available for evaluation; and that, in the case of the claims relating to premature labor and abortion, respectively, no document was "applicable" or available (J.A. 5).

It is clear that this report was a basic motivation, if not the principal one, for the FDA order withdrawing approval of the NDA for Lutrexin. In any event the opinion of the panel was the only information before FDA which suggested that Lutrexin was not effective.

In its petition for a writ of certiorari in this case (No. 72-394) the Government refers to "the mass of material" submitted to FDA by HW&D, declaring that "most of that material had previously been considered by the NAS-NRC panel" (Pet. 9), and thereafter stating that the NAS-NRC panel had "little difficulty" concluding that the studies submitted "did not meet the medical community's standard of adequacy" (Pet. 14).

In fact, only four of the fourteen studies (of which eleven were published) were considered by the NAS-NRC panel, *viz.*, two studies not identified by the panel by name, the study by G. E. Hayden, *Relief of Primary Dysmenorrhea* and that by S. S. Jones, *Lutrexin, A Drug For Relief Of Dysmenorrhea* (J.A. 7-8). None of the other studies (J.A. 86-172) was considered,* nor, of course, were the affidavits of experts which were subsequently furnished to the District Court in Baltimore and to FDA (J.A. 32-72).

It was therefore important to HW&D to inquire into the decision-making process which led to the withdrawal order. In response to inquiry by HW&D, dated August 18, 1969, the Acting Associate Director of Information

* Two of the studies were completed after the panel reported.

for Public Services of the Department of Health, Education and Welfare, replied, by letter of September 18, 1969 (J.A. 18-20), that neither FDA nor the Department has "any report of any deliberations, minutes, notes, or other material of the National Academy of Sciences-National Research Council Panel . . ."; that neither FDA nor the Department "has any statement, other than the reports themselves, reflecting the view of each member of the panel concerning the effectiveness of Lutrexin . . ."; [7] that "other than the references listed under the heading, Documentation, by the Panel in its reports on Lutrexin . . . we do not know what medical or scientific literature was relied upon by the Panel"; and that FDA "has not conducted any independent clinical study or other scientific investigation of Lutrexin . . . at any time."

Thus, one of the principal supports of the FDA withdrawal order was formulated without the benefit of most of the available literature on Lutrexin and we do not know how or by what vote the panel reached its decision. Had the NAS-NRC panel had the benefit of such literature reflecting the conclusions that the clinical experts have reached, its evaluation might well have been that the drug is effective as claimed. The final evaluation of FDA might therefore have been entirely different. All that HW&D asks this Court, therefore, in this brief, is that the decision of the Fourth Circuit be affirmed so that the experts can be examined at a hearing to determine the validity and significance of their studies and of the opinions expressed in their affidavits. Certainly, more information should be made available on the manner in which the NAS-NRC panel reached its conclusions, particularly in the light of the statement of Dr. Allen, a member of the panel, that Lutrexin con-

[7] This point was important because, of the five members of the panel, only two were specialists in obstetrics and gynecology.

tains a biologically active component which has a relaxing effect on the uterus of laboratory animals and women and should remain on the market (J.A. 47, 48).

In *USV Pharmaceutical Corp.* v. *Secretary of Health, Education, and Welfare*, 466 F.2d 455 (D.C. Cir. 1972), as the Government states in its brief in the instant case, it was held that "the Commissioner may not simply rely on the reports of the NAS-NRC panels to call upon the holder of an NDA issued prior to October 10, 1962, to produce evidence of effectiveness establishing his right to a hearing or lose approval of the NDA." (Br. p. 32, footnote 32). The court thought that "it was incumbent upon the Commissioner . . . to state facts and reasons showing at least prima facie that the evidence before him raised no material issue of fact which would justify a hearing"; and that, under Rule 56 of the Federal Rules of Civil Procedure (to which FDA has likened its regulations in 21 CFR 130.14) "the moving party has the burden of presenting evidence that establishes his right to summary judgment as a matter of law. . . ." 466 F.2d at 461.

FDA has presented no facts to show an alleged lack of substantial evidence of effectiveness. As we have stated, the sole "evidence" of lack of effectiveness is the opinion of the NAS-NRC panel that the drug is only "possibly effective." In the *USV* case above cited, the Court of Appeals characterized certain NAS-NRC panel reports as "cryptic and conclusory, without any statement of supporting facts." 466 F.2d at 461. The report on Lutrexin fits this description. All of the affirmative evidence before both the panel and FDA indicates that the drug is effective.[8] What FDA has done, therefore, is to place the burden of proving the existence of sub-

[8] Summary and explanation of the medical data is found in Point I, A and B, *infra*.

stantial evidence upon HW&D without even giving the Company an opportunity to be heard.

Under FDA's former regulations[9] which correctly followed the statute by granting hearings on NDA withdrawals, the burden of proof was on FDA to prove that there was a lack of substantial evidence of effectiveness for the drug involved. This is clear from *Bell* v. *Goddard*, 366 F.2d 177, 181 (7th Cir. 1966), which was decided some four years after enactment of the Drug Amendments of 1962.

Now, however, not only does the Government maintain that it is incumbent upon HW&D to show the existence of an issue of material fact but goes further and claims in effect that HW&D must show the existence of substantial evidence of effectiveness in order to obtain a hearing.

I

THE STUDIES AND AFFIDAVITS SUBMITTED BY HW&D IN ITS REQUEST FOR A HEARING RAISED GENUINE AND SUBSTANTIAL ISSUES OF FACT REQUIRING A HEARING.

Introduction

In *Hynson, Westcott and Dunning, Incorporated* v. *Finch*, (C.A. No. 21112, D. Md. 1970),[10] HW&D was prepared to offer factual proof at a trial, and is prepared to do so in a hearing before FDA, to support its contentions that Lutrexin is both safe and effective. This proof was and is available in the form of expert testimony by physicians who have studied and used Lutrexin

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[9] 21 CFR Section 130.14, revised as of January 1, 1969. These provisions were replaced by the present Section 130.14 in May, 1970.

[10] A summary of the Complaint in that cause appears at J.A. 15.

extensively, as well as in the form of medical investigations. The proper and legally required method of presenting such proof should have been at a trial or adjudicative hearing where the expert testimony could have been tested by cross-examination.

Unfortunately, however, this court does not have before it for review an order based upon any evidence adduced at a trial or hearing. The order is based upon a rejection by FDA of the evidence proffered by HW&D, in its renewed request for a hearing, dated October 16, 1970 (J.A. 24). The affidavits, studies, and other data, which will be summarized below, show that there exists solid evidence to support HW&D's claims of safety and effectiveness, evidence which clearly raises questions of fact which should be resolved in an adjudicative administrative hearing.

The effect of the failure to hold a hearing is two-fold: (1) the order before the court cannot be accorded the usual deference due to a determination by an expert administrative agency based upon substantial evidence adduced at a hearing; and (2) the court must itself determine the complex medical issues of fact before it, or as the Court of Appeals held, remand the case to the agency for determination after appropriate hearing.

A. Summary and Explanation of the Medical Data Relating to the Nature of the Product and Its Safety.

Lutrexin is indicated for use in the treatment of selected cases of premature labor, second and third trimester threatened abortion, and dysmenorrhea. The difference between abortion and premature labor is primarily one of the length of gestation. The term "abortion" or "threatened abortion" is generally used to refer to expulsion or threatened expulsion from the uterus of the product of conception before twenty weeks of the

pregnancy have passed; "premature labor" generally refers to the commencement of labor in the latter stage of the pregnancy but prior to term.

The term "dysmenorrhea" refers to the various symptomatic disorders suffered by some women during or just prior to menstruation, such as, cramps, backache, headache, nausea, vomiting, and malaise.

Premature labor, abortion, and dysmenorrhea are generally thought to result, at least in part, from abnormal or untimely contractions of the musculature of the uterus. The purpose of Lutrexin therapy is to quiet the uterus to prevent, in premature labor, a too-early birth, and in dysmenorrhea, to relieve cramping and associated symptoms.

(1) *The Product*

The active ingredient or uterine relaxing factor (URF) in Lutrexin is extracted from the corpus luteum of sow ovaries. The corpus luteum, in animals as well as human beings, is composed of cells formed after ovulation, i.e., after release of an egg from the ovary. In addition to the URF the corpus luteum secretes other hormones essential for the maintenance of pregnancy, including progestin (progesterone). It has been conclusively demonstrated, however, that the uterine relaxing factor or active ingredient in Lutrexin is a distinct entity whose quieting effect on the human uterus is not due to the presence of progesterone in the product (J.A. 148, 152-153; J.A. 153, 156).

(2) *Affidavits*

The safety of Lutrexin has not been questioned. Nor can it be. The affidavits of Doctors Bickers, Gratton, Majewski, Rezek, Gray and Trythall, the letter of Dr. Willard M. Allen,[11] as well as the medical studies set

[11] J.A. 32, 36, 39, 43, 54, 50, 47.

forth in the appendix (J.A. 86 *et seq.*), and discussed below, demonstrate conclusively that Lutrexin is safe.

Dr. Gratton, for example, states in his affidavit: ". . . there is no question that Lutrexin is safe, for I have administered up to 36,000 units of the drug to many patients in an eight to twenty-four hour period with no side effects to mother or child" (J.A. 37). Dr. Majewski has administered "4000 units of the drug stat., and 1000 units hourly thereafter until uterine contractions cease" with no side effect (J.A. 40-41). Dr. Rezek concludes to the same effect after prescribing "up to 12,000 units hourly for seven days" (J.A. 44-45). All told, Doctors Bickers, Majewski, Rezek, and Gratton have treated over two thousand patients with Lutrexin, with no side effects to patient or infant (J.A. 33, 40, 44, 36).

The expertise in obstetrics and gynecology of affiants Bickers, Gratton, Majewski, and Rezek is obvious from a reading of their affidavits and curricula vitae,[12] and needs no further elaboration. Their extensive study and use of Lutrexin also need not be restated. All state in their sworn affidavits that based upon their study of the literature on Lutrexin, described below, upon knowledge of the opinions of their expert colleagues, and upon their personal experience administering Lutrexin to several thousand patients, the product is safe.

(3) *Medical Literature*

Reports on Lutrexin have been made in the literature by Doctors Gratton, Majewski,[13] Rezek, Jones and Smith, Krantz, et al., Felton, et al., and S. Jones (J.A. 86, 92-111, 112-121, 160, 148, 153, 167).

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[12] J.A. 32 *et seq.*

[13] Dr. Gratton's paper and the 1968 paper of Dr. Majewski have not been published.

Krantz et al., in a study published in 1950 (J.A. 148), developed a laboratory method for showing the uterine-relaxing effect of aqueous extracts of corpus luteum in live guinea pigs. This method is important, for it forms the basis for the establishment of a standard unit of dosage for the uterine relaxant activity of Lutrexin. The method is a simple one: the guinea pig is treated with a hormone to induce an artificial state of pregnancy. The uterus of a guinea pig so treated demonstrates a regular pattern of contractions. To measure this activity, and the effect of an injection of lututrin (the active ingredient of Lutrexin), the pig is anesthetized, its uterus is lifted partially out of the abdomen and attached to a lever, which records the level of contractions.

In the study, Krantz et al. injected an aqueous corpus luteum extract into the jugular veins of seventeen guinea pigs prepared as stated above. The recordings of uterine contractions showed a marked reduction in uterine activity in all of the animals injected. As a result of the work of Krantz et al., it was possible to establish a standard unit of URF activity: the minimal amount which, when injected intravenously into the hormone-treated guinea pig, effects a 90 per cent reduction in the height of spontaneous uterine contractions for a period of ten minutes.[14] Thus, the clinician is provided with a standardized unit of Lutrexin, which permits him to administer a "known" amount to his patients. He can then adjust the dosage according to clinical response of the patient.

The published studies of Rezek, and Jones and Smith demonstrate the safety of Lutrexin in the treatment of dysmenorrhea in women. Dr. Rezek treated a total of 298 dysmenorrheic patients with substantial doses of Lutrexin and "no undesirable by-effects of any kind were

[14] See papers by Felton et al. and Jones and Smith, J.A. 153, 160.

noticed, although some patients were observed for as long as eleven periods" (J.A. 112, 117). Jones and Smith treated 90 dysmenorrheic women with Lutrexin, and in addition gave large doses to 10 men to test the toxicity of Lutrexin:

> "In testing the toxicity of the drug, as much as 10,000 units in a single dose was given to 10 men with no untoward results. Two women under observation have also taken 10,000 units at one time and, although they were somewhat drowsy for several hours, no other effects were observed" (J.A. 160, 162).

The reports of Gratton, Majewski, Rezek, Gray, and Trythall involve treatment of over four hundred pregnant women with Lutrexin, with no reported side effects (J.A. 87, 92-111, 112, 131, 135).

On the basis of the foregoing studies published in the medical literature, and on their own experience and discussions with colleagues, Doctors Bickers, Gratton, Majewski, and Rezek concluded in their affidavits that Lutrexin is safe for use in treatment of premature labor (and abortion) and dysmenorrhea.

To date, the FDA has offered no refutation of the evidence proffered by HW&D on the question of the safety of Lutrexin.

B. Summary and Explanation of the Medical Data Relating to the Effectiveness of the Product.

(1) *Affidavits*

Doctors Bickers, Gratton, Majewski, Rezek, Trythall and Gray state in their affidavits that, based upon their study of the medical literature on Lutrexin, reviewed below, upon their own study and use of Lutrexin, and upon knowledge of opinions of their colleagues, Lutrexin is effective for use in the treatment of second and third

trimester threatened and habitual abortion and premature labor (J.A. 34, 37, 40, 44, 51, 55). Doctors Bickers and Rezek, upon the same basis, state in their affidavits that Lutrexin is effective for use in the treatment of dysmenorrhea (J.A. 34, 44).

All affiants have had extensive experience in the use of Lutrexin: Doctors Bickers, Gratton, Rezek, Majewski, Gray, and Trythall have used Lutrexin in treatment of pregnancy problems for an average of 14 years, involving over 2,000 patients; Doctors Bickers and Rezek have used Lutrexin in treatment of 1,500 dysmenorrheic patients for over 15 years.

It is submitted that based upon the affidavits alone, HW&D demonstrated in its request for a hearing after dismissal of its action in the Maryland District Court the existence of genuine and substantial issues of fact requiring a hearing. The Commissioner's bare statement that the affidavits cannot be accepted because of a failure to identify adequate and well-controlled investigations (J.A. 74) is controverted by statements in the affidavits. Thus, Dr. Gratton stated in his affidavit:

> "Studies such as the one reported in Exhibit B [J.A. 87], utilizing the past histories of the patients as controls . . . are proof of the effectiveness of Lutrexin. Such studies . . . cannot be dismissed on the ground that they are valueless because they do not use a double-blind placebo type of investigation. The latter type of investigation is inconceivable from the standpoint of ethics and morality where, as here, there exists a high risk of mortality and the physician is testing a drug (Lutrexin) which is clinically-proven to be effective" (J.A. 37).

Similarly, Dr. Majewski stated in his affidavit:

> "The method of investigation utilized in my studies (Exhibit B, C, and D) [J.A. 92-111] *viz.*, use of the patients as their own controls, or use as a control of

statistics reflecting the experience with other patients with no treatment, together with the general clinical experience of the physician, constitute the only humane approach to the study of the effectiveness of a drug for use in threatened abortion and premature labor. These complications of pregnancy carry a high risk to the life of the fetus and perhaps the mother. Use under such conditions of a double-blind, placebo type of investigation would be unethical and immoral, where, as here, there exists a drug (Lutrexin) clinically-proven to be of value in the treatment of the affliction involved" (J.A. 41).

(2) *Medical Literature*

(a) *Historical Controls*

FDA's regulations defining "adequate and well-controlled studies" require that a medical investigation contain a method of selection of the subjects that . . . provides a comparison of the results of treatment . . . [using the drug under investigation] with a control in such a fashion as to permit quantitative evaluation" (21 C.F.R. 130.12(a)(5)(ii)(a)(4); J.A. 488). One method of control acceptable to the agency is historical control:

> "Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen . . . the effectiveness of which is established" (21 C.F.R. 130.12(a)(5)(ii)(a)(4)(iv); J.A. 488-489).

It cannot be gainsaid that premature labor and threatened and habitual abortion are conditions involving a "high and predictable mortality" as well as conditions "where morbidity is predictable." If premature contractions of a gravid uterus are not halted, a dead fetus is almost certain.

The necessity of performing certain tests using historical controls is described by Dr. Allen who was a member of the NAS/NRC panel which reviewed Lutrexin.[15]

> "There is a good deal of uncertainty regarding what type of study should be carried out in order to fully establish the validity of the results. In these studies the patient herself serves as the control; the results in the pregnancies prior to the treated pregnancy are compared with the results in the treated pregnancy. A supposedly better method of study which is popular today would utilize the placebo method; one patient receives the hormone and the next patient the placebo, the investigator not knowing which patient received the placebo until the study is complete. This type of study is now so 'sacred' that any other type is often not recognized as investigative. However, there are many clinical problems in which this type of study violates the rules of clinical morality as

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[15] Dr. Allen also is on record in support of the continued marketing of Lutrexin. He has stated, in a notarized letter to HW&D:

> "Lutrexin contains a biologically active component (as yet unidentified structurally) which has a relaxing effect on the uterus of laboratory animals and women". * * * "The clinical evidence which you have submitted [to me] . . . does indicate that Lutrexin is beneficial in the three conditions for which it is recommended. The evidence also indicates that Lutrexin is not harmful or dangerous either to the patient or to the fetus. You have submitted no evidence that Lutrexin is ineffective, nor do I know of any evidence in the medical literature indicating that it is ineffective." * * * "Lutrexin, since it contains an active principal which relaxes the uterus, should be available for the treatment of premature labor . . ." J.A. 47, 48.

well as common sense. Let us consider some disease in which the risk of death is appreciable, lobar pneumonia, for example. No clinician could risk treating alternate cases with an antibiotic and a placebo. In such a study the risk of death while receiving the placebo might be as much as 25 per cent. In the study of habitual abortion the risk of death to the fetus in utero is between 80 to 90 per cent. It seems to me that one no longer has the right to use a placebo as a control because the data already available from the studies in which the patient serves as her own control indicate that the fetal losses are reduced from 80 or 90 per cent to 25 per cent or perhaps less." [16]

(b) *HW&D's Investigations*

In Dr. Gratton's study,[17] which involved habitual aborters, the patients were used as their own controls, and the results of Lutrexin treatment vis a vis prior untreated pregnancies were statistically evaluated:

". . . in the 219 patients with a total of 446 pregnancies, there were only 46% live births prior to the use of Lutrexin. Following the administration of Lutrexin, the percentage of live births in these same patients was 79.8% with a probability of .001. Probabilities ranging from .001 to .05 were observed in women with one to five pregnancies who had been treated with Lutrexin" (J.A. 88).

In Dr. Majewski's first two studies,[18] which involved premature labor, the results were compared with the documented history of premature births in the hospital where the study was performed:

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[16] J.A. 121, 127-128. This paper is not a report on Lutrexin.

[17] J.A. 86.

[18] J.A. 92, 99.

"The hospital wherein the study was conducted has . . . a premature birth rate of 9.7 per cent by length of gestation and 6.2 per cent by weight. During a four-month period in 1953, the premature birth rate by history was 9.7 per cent in 1601 deliveries. During the same period, there were 101 premature births by weight, or 6.3 per cent. During this study there were, in a comparable period during 1954, 154 births premature by history in a total of 1631 deliveries, for a percentage of 9.4. In our series of patients using the uterine relaxing factor [Lutrexin] the number of premature deliveries by weight was reduced during these four months to 80 (4.9 per cent), a saving of 21 premature deliveries" (J.A. 94).

In Dr. Majewski's second study,[19] which is a continuation of the first study, the comparison was enlarged to one of the total number of premature survivals, stillbirths and neonatal deaths during the 15-month period the study was in progress. In Dr. Majewski's third study the results were compared statistically with the results of prior untreated pregnancies (J.A. 106).

The studies by Drs. Rezek, G. Jones et al., and S. Jones show the clinical effectiveness of Lutrexin (J.A. 112, 160, 167). The studies of Drs. Rezek and G. Jones present laboratory confirmation of the biological activity of Lutrexin in humans (J.A. 116, 162-163).

It is clear from the foregoing summary of the affidavits and studies submitted in HW&D's request for a hearing and from the Commissioner's factual criticisms of the affidavits and studies (J.A. 72)[20] that genuine

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[19] J.A. 99.

[20] We have shown in detail in our brief in No. 414 (pp. 33-35) that FDA's critique of the studies and affidavits, as held by the Court below, ". . . at most, . . . merely create a genuine question of fact to be resolved at a hearing upon proper evidence" (J.A. 180).

and substantial issues of disputed fact exist that require a hearing. As clearly appears from the above summary, HW&D's evidentiary showing cannot be dismissed as being merely "testimonial" in nature.

II

FDA'S "SUMMARY JUDGMENT" REGULATIONS ARE INHERENTLY UNFAIR AND AS APPLIED IN THE INSTANT CASE DENIED HW&D DUE PROCESS OF LAW.

A. The Regulations

A proceeding under FDA's "summary judgment" regulations (J.A. 490-491) is initiated by a notice from the Commissioner of an opportunity for a hearing on a proposal to withdraw approval of an NDA under Section 505(e) of the Act (J.A. 479). The regulations require a manufacturer responding to such a notice to submit a request setting forth ". . . specific facts showing that there is a genuine and substantial issue of fact that requires a hearing" (J.A. 491). The request must identify "adequate and well-controlled clinical investigations" to support claims of effectiveness for the drug (J.A. 491). If the Commissioner determines that the request does not identify any such studies, he will deny the request for a hearing because the request did not show that there is "a genuine and substantial issue of fact" that requires a hearing.

The regulations are unfair on their face. They do not provide for the submission by or on behalf of the Commissioner of any evidence to rebut the manufacturer's data or to show that no genuine and substantial issue of fact exists. They do not provide the manufacturer an opportunity to refute the Commissioner's findings that the medical studies submitted in the request for a

hearing are not adequate and well-controlled and do not raise a genuine and substantial issue of fact requiring a hearing. Finally, no attempt is made in the regulations to provide for a separation of the prosecutorial and judging functions of the Commissioner.

B. Decision Of The Court Of Appeals.

The Government states in its brief that the Court of Appeals upheld the validity of the Commissioner's "summary judgment" regulations (Br. 24, 30, 33 (n. 23)). More accurately, the Court held that while it may be assumed that the regulations may be applicable to this case, the Commissioner's application of them to deny HW&D a hearing was arbitrary and not in conformity with due process and the Administrative Procedure Act (J.A. 177-179). Thus, the court said:

> ". . . we are of opinion the showing of the appellant was such that, under a reasonable construction of the Commissioner's own regulations, as well as under familiar principles of due process, and the requirements of the Administrative Procedure Act, it was entitled to an impartial hearing before its NDA was withdrawn" (J.A. 179).

The Court held that the Commissioner's criticisms in his withdrawal order of HW&D's medical studies indicate that disputed issues of fact exist requiring a hearing:

> "Assuming that all the objections by the Commissioner to these clinical studies, conducted as they were by competent medical authorities, may have some validity, they do not justify a final conclusion, made *ex parte*, without a hearing, that it 'clearly appears' that there is no genuine issue of fact on the effectiveness of Lutrexin, which is the test under the Commissioner's own regulation for denial of a hearing; at most, they merely create a genuine question of fact to be resolved at a hearing upon proper

evidence. Whether the studies were as controlled as they might have been and whether there was a failure in these studies as published to fill in all the details the Commissioner might think appropriate are matters that could be developed at a hearing, after the authors were examined and the reliability of the investigations further inquired into" (J.A. 180).

C. The Unfairness of the "Summary Judgment" Regulations.

FDA has characterized its procedural regulations governing hearings under Section 505 of the Act as ". . . similar in some respects to a trial court's granting of a motion for summary judgment when there are no legally relevant controverted facts to be decided" (Br. 20-21). The only similarity between FDA's procedure and that contemplated by Rule 56 of the Federal Rules of Civil Procedure is the concept of the requirement of a genuine and substantial issue of fact as a condition for an adjudicative hearing. None of the safeguards carefully elaborated by rulings of this and lower federal courts in Rule 56 decisions has been incorporated into FDA's procedures.

(1) *Lack Of An Impartial Decision-Maker*

A fundamental requirement of due process in administrative proceedings is an "impartial decision maker." *Goldberg* v. *Kelly*, 397 U.S. 254, 271 (1970); *Wong Yang Sung* v. *McGrath*, 339 U.S. 33, 41-45 (1950). This requirement was clearly not met in the administrative proceedings before FDA. Nor, as presently constituted, do the regulations meet it. (21 CFR 130.14; J.A. 490). Under the regulations, the Commissioner, acting in effect as a party litigant or advocate, moves for a summary disposition of the NDA withdrawal proceeding by issuing a notice of an opportunity for a hearing. In the

notice, in this case, the Commissioner stated that the information before him "does not provide substantial evidence of effectiveness of . . . [Lutrexin] for its recommended uses" (J.A. 12) and that if a final order were issued withdrawing NDA approval, the drug ". . . would be subject to regulatory proceedings" (J.A. 13). After submission of HW&D's request for a hearing, with attached medical data in support thereof, the Commissioner-advocate judges whether the submission raises a genuine and substantial issue of fact requiring a trial-type hearing. This commingling of the functions of prosecutor and judge is patently unfair. As stated in the Report of the President's Committee on Administrative Management, quoted favorably in *Wong Yang Sung*, supra at 42:

> "This not only undermines judicial fairness; it weakens public confidence in that fairness. . . . [D]ecisions affecting private rights and conduct lie under the suspicion of being rationalizations of the preliminary findings which the . . . [agency], in the role of prosecutor, presented to itself" (Administrative Management in the Government of the United States, Report of the President's Committee on Administrative Management, 36-37 (1937)).

The Government cites in its brief in support of its hearing procedures the practice of the Federal Trade Commission and the National Labor Relations Board in this regard, stating that their procedures are "similar" to FDA's (Br. 23).[21] The procedures of those agencies relating to motions for summary judgment are, in fact, dissimilar to FDA's for they provide for the very safeguard we have shown to be missing in the FDA procedures, *viz.*, an impartial decision-maker whose sole role is to judge (16 CFR 3.24; 29 CFR 102.24, 102.25). The

[21] The Administrative Conference recommendation referred to in the Government's brief (p. 23) was that summary judgment procedures similar to Rule 56 of the Federal Rules of Civil Procedure be adopted. This FDA has not done.

trial examiner in such cases receives evidence from counsel for the agency and the private party on the question of whether disputed facts exist, and renders an impartial decision thereon. The procedures adopted by the FTC and NLRB are the type contemplated by the Administrative Procedure Act. The Final Report of the Attorney General's Committee on Administrative Procedure states in part:

> "These types of commingling of functions of investigation or advocacy with the function of deciding are thus plainly undesirable. But they are also avoidable and should be avoided by appropriate internal division of labor. For the disqualifications produced by investigation or advocacy are personal psychological ones which result from engaging in those types of activity; and the problem is simply one of isolating those who engage in the activity. Creation of independent hearing commissioners insulated from all phases of a case other than hearing and deciding will, the Committee believes, go far toward solving this problem at the level of the initial hearing provided the proper safeguards are established to assure the insulation. * * *" Rep. Atty. Gen. Comm. Ad. Proc. 56 (1941), S. Doc. No. 8, 77th Cong., 1st Sess. 56 (1941).

The Government's constant refrain that its summary disposition regulations are essential in order to enable the agency to carry out the functions mandated to it by Congress cannot serve to justify dispensing with impartial decision making. As this court stated in applying the separation of functions requirement of the Administrative Procedure Act to proceedings before the Immigration Service:

> "Nor can we accord any weight to the argument that to apply the Act to such hearings will cause inconvenience and added expense to the Immigration Service. Of course it will, as it will to nearly

> every agency to which it is applied. But the power of the purse belongs to Congress, and Congress has determined that the price for greater fairness is not too high. The agencies, unlike the aliens, have ready and persuasive access to the legislative ear and if error is made by including them, relief from Congress is a simple matter" (*Wong Yang Sung, supra* at 46-47).

The Court of Appeals for the District of Columbia Circuit in a recent decision reviewed an order of the Commissioner withdrawing approval of the NDA for a drug pursuant to the "summary judgment" regulations. The court stated:

> "The Commissioner acted pursuant to 21 C.F.R. § 130.14, the regulation establishing a summary judgment procedure for the Food and Drug Administration. This regulation is modeled after Rule 56 . . . A vital distinction, however, is that the Commissioner here was not an impartial arbiter of the contentions of opposing parties, but was himself the moving party undertaking to support his own proposed order" *USV Pharmaceutical Corp.* v. *Secretary of Health, Education and Welfare,* 466 F.2d 455, 461 (1972).

(2) *Burden of Proof in Summary Judgment Proceedings*

We show under Point III that the burden of proof in withdrawal proceedings pursuant to section 505(e) of the Act is on the Commissioner. It is also settled beyond peradventure that the party moving for summary judgment has the burden of ". . . showing the absence of a genuine issue as to any material fact . . ." *Adickes* v. *S. H. Kress and Company,* 398 U.S. 144, 157 (1970). Under FDA's regulations, the Commissioner has no burden of showing the absence of disputed facts; rather the party opposing the motion for summary judgment has the burden of proving the existence of a genuine issue

of fact. This is a clear perversion of the concept of summary judgment.

This court has outlined the conditions under which a movant is entitled to a grant of his motion for summary judgment:

> ". . . Rule 56 authorizes summary judgment only where the moving party is entitled to judgment as a matter of law, where it is quite clear what the truth is, . . . no genuine issue remains for trial . . . the purpose of the rule is not to cut litigants off from their right of trial by jury if they really have issues to try." *Sartor* v. *Arkansas Natural Gas Corp.*, 321 U.S. 620, 627 (1944).

The Commissioner acting under his form of summary judgment met none of these conditions. Indeed, since the Commissioner contented himself with merely a criticism of HW&D's medical studies and affidavits, and did not submit evidence showing the absence of a genuine issue of fact, HW&D was entitled to judgment as a matter of law (or at the least a hearing). The Commissioner's burden was well-described by the Court of Appeals for the District of Columbia Circuit:

> "The petitioner's applications had been approved, pursuant to 21 U.S.C.A. § 355(b) (1961), but now, under 21 U.S.C. § 355(e), the Commissioner proposed, without a hearing, to withdraw that approval on the basis of a new standard and new information, together with the evidence available when approval was originally granted. In this situation we think it was incumbent upon the Commissioner, before calling upon the petitioner for additional evidence establishing a right to a hearing, to state *facts* and reasons showing at least prima facie that the evidence before him raised no material issue of fact which would justify a hearing. This view of the Commissioner's burden is consistent with the prac-

tice under Rule 56 of the Federal Rules of Civil Procedure. *Under that rule the moving party has the burden of presenting evidence that establishes right to summary judgment as a matter of law*; and he may not, by the bare assertion that he is entitled to summary judgment, shift to his opponent the burden of establishing the contrary" (Emphasis supplied). *USV Pharmaceutical Corp.* v. *Secretary of Health, Education and Welfare*, 466 F.2d 455, 461 (1972).

D. Due Process.

The Court of Appeals held that denial of a hearing to HW&D was contrary to applicable principles of due process and the Administrative Procedure Act and to a reasonable construction of the Commissioner's own regulations (J.A. 179).

This holding follows the decisions of the Supreme Court in *Goldberg* v. *Kelly*, 397 U.S. 254 (1970) and *ICC* v. *Louisville & N.R. Co.*, 227 U.S. 88 (1913). As stated by Mr. Justice Brennan in *Kelly* "In almost every setting where important decisions turn on questions of fact, due process requires an opportunity to confront and cross-examine witnesses" (397 U.S. at 269). The decision below and our analysis of the evidence submitted by HW&D (Point I) demonstrate the applicability of these cases here. We have already shown in the brief for Cross-petitioner in No. 72-414, that such cases require a hearing on the jurisdictional questions (Brief for Cross-Petitioner pp. 31-38).

Likewise, the facts at issue here (in No. 72-394) are adjudicative facts, just as are those involved in the jurisdictional questions, i.e. "those to which the law is applied in the process of adjudication. . . . They relate to the parties, their activities, their properties, their business." 3 Davis, Administrative Law Treatise, § 15.03,

p. 353. They are thus distinguished from legislative facts which are those upon the basis of which law and policy have been previously established.

The question of whether the materials submitted by HW&D constitute "substantial evidence" as defined in Section 505(d) of the Act can only be determined upon the basis of a trial-type hearing. Davis, Administrative Law Treatise, 1970 Supplement, Sections 7.01, 7.04. They relate only to the business of Hynson, Westcott & Dunning in the marketing of Lutrexin, and to its labeling, and are not pertinent to any other drugs or their status under the Act. Professor Davis' view is entirely consistent with the decisions of this Court in *Kelly* and *Louisville & N.R. Co., supra.*

III

RESPONDENT HW&D IS ENTITLED BY LAW TO AN EVIDENTIARY, TRIAL-TYPE HEARING UPON THE QUESTION OF WHETHER THERE IS SUBSTANTIAL EVIDENCE OF THE EFFECTIVENESS OF LUTREXIN.

A. The Hearing Requirement Of The Statute And The Alleged Incapacity Of The Agency To Meet Anticipated Demands For Hearings If It Is Enforced.

The Government repeatedly sounds the alarm that, if FDA were required to provide HW&D a hearing the agency would have to grant a hearing before withdrawing approval for each of the some 3500 products reviewed by the panels of the National Academy of Sciences-National Research Council (NAS-NRC) and that "the agency would be mired in hearings for years" (Br. 19). The same theme recurs in the Government's brief in *Bentex.*[22]

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[22] *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72-555 (J.A. 270), one of the cases consolidated with the instant case (No. 72-394).

We do not maintain that a hearing would be required in every such case, even under the old regulations which were superseded by the so-called "summary judgment" regulations of May 8, 1970.

Thus, a hearing is not required where, even if petitioner's contentions were proved, it would avail him nothing because the legality of the order attacked would not be effected. *Dyestuffs & Chemicals, Inc.* v. *Flemming*, 271 F.2d 281 (8th Cir., 1959), cert denied, 362 U.S. 911 (1960). Nor is a hearing required where no fact question is involved. *Sun Oil Co.* v. *FPC*, 256 F.2d 233 (5th Cir., 1958), cert denied, 358 U.S. 872. This is obviously not true of HW&D's contentions here, as we show under Point I. The affidavits and medical literature submitted to the Commissioner are, at the least, sufficient to raise an issue of material fact on the question of substantial evidence, as the Court of Appeals held.

We do not know in how many of the cases involved, a hearing would be required since each case must be evaluated on its own facts. We know, however, that no hearing has been held to date under the 1970 "summary judgment" regulations and it seems apparent that the Commissioner intends to grant such hearings only in extraordinary situations, if this Court sustains the 1970 restrictive regulations (21 CFR 130.14, J.A. 490-491). The Government states, in Footnote 15 of its brief in the instant case (No. 72-394) that:

> "The nature of the problems is such that formal hearings are not likely to be needed in many instances. If studies exist that appear on their face to constitute adequate and well-controlled investigations as defined in the regulations, the Commissioner would, in the absence of unusual circumstances, find the drug effective and not pursue withdrawal of its NDA. If the manufacturer is unable to make a

prima facie showing that such studies exist, a hearing would be useless" (Br. p. 20).

Thus, FDA in effect equates the concept of *prima facie* showing with a showing of substantial evidence; conversely, it equates the statutory concept of "lack of substantial evidence with its idea of a lack of a *prima facie* showing." Obviously, if this approach is legally justifiable, a hearing would rarely be required and the merits of each case could be tried *ex parte*, on motion, as FDA has done in the instant case. But this was clearly not the intent of Congress. It is not supported by the language of the statute itself or its legislative history.

In passing upon an NDA the Secretary (Commissioner) is required, under Section 505(c), (21 U.S.C. 355(c)), either (1) to approve the application or "(2) give the applicant notice of an opportunity for a hearing. If the applicant elects to accept the opportunity for a hearing by written request within thirty days after such notice, *such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree*" (emphasis supplied).

It seems perfectly apparent that under such an explicit provision the Commissioner may not avoid a hearing simply by deciding *ex parte* that there is is a lack of substantial evidence of effectiveness.

Certainly, there is no sound reason for saying that the right to a hearing in a withdrawal proceeding under Section 505(e)(3) is any less firm than under Section 505(c)(2), above quoted in part. Senator Eastland, the Chairman of the Senate Committee on the Judiciary, in explaining to the Senate the withdrawal provision of S.1552, as finally enacted, stated:

"Withdrawal of approval of any new drug application on the basis of the foregoing grounds would

be preceded by a hearing and an order with findings on the basis of the record." [23]

One of the "foregoing grounds" referred to by Senator Eastland is that upon the basis of which FDA acted in the instant case (Section 505(e)(3)).

Even if, because of staff or financial limitations, FDA could not handle expeditiously the case load of NDA withdrawal proceedings where hearings are required by the statute, that would constitute no valid reason for denying such hearings. Section 505(e) of the Act directs the Commissioner to give due notice and opportunity for hearing prior to withdrawal of approval of an NDA. FDA's position herein would, in effect, read this provision out of the statute. This court has repeatedly held that the authority of an administrative agency is circumscribed by the powers granted to it by Congress.

Thus, in *Manhattan General Equipment Co.* v. *Commissioner of Internal Revenue*, 297 U.S. 129, 134 (1936) the court said:

> "The power of an administrative officer or board to administer a federal statute and to prescribe rules and regulations to that end is not the power to make law, for no such power can be delegated by Congress, but the power to adopt regulations to carry into effect the will of Congress as expressed by the statute. A regulation which does not do this, but operates to create a rule out of harmony with the statute, is a mere nullity. * * *

This statement was quoted with approval in *Dixon* v. *United States*, 381 U.S. 68, 74 (1965).

In *Stark* v. *Wickard*, 321 U.S. 288, 309 (1944) the court said:

> "When Congress passes an Act empowering administrative agencies to carry on governmental activities,

[23] 108 Cong. Rec. 16,304, August 23, 1962.

> the power of those agencies is circumscribed by the authority granted."

The Food and Drug Administration itself was admonished in *62 Cases etc.* v. *United States*, 340 U.S. 593, 600 (1951), that:

> "In our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop."

Unless, therefore, there is no issue of material fact raised by the evidence submitted in a withdrawal proceeding under Section 505(e), the Commissioner may not deny a hearing under the statute. The contention that FDA could not hold all the hearings which would be necessary if Congress' directions were followed is no excuse, even if true.

The Court addressed itself to this point in *Ohio Bell Telephone Co.* v. *Public Utilities Commission of Ohio*, 301 U.S. 292, 305 (1937) when it said, per Mr. Justice Cardozo, with reference to the failure of the Commission to honor the requirement of a hearing:

> "There can be no compromise on the footing of convenience or expediency, or because of a natural desire to be rid of harassing delay, when that minimal requirement has been neglected or ignored."

We quote elsewhere the opinion of this court in *Wong Yang Sung* v. *McGrath*, 339 U.S. 33, 46-47 (1950), that the argument that application of the Administrative Procedure Act to immigration hearings will cause inconvenience and added expense to the Immigration Service, cannot be accorded any weight; that Congress has determined that the price of greater fairness is not too high; that the agencies have access to Congress; and if error has been made, Congress can correct it. Congress later

exempted the Service from the APA and it can modify the hearing requirements of Section 505 if it so desires.

The Court of Appeals for the Third Circuit, in a situation where the Federal Power Commission rejected proposed tariff changes without a hearing required by statute, declared:

> "We can understand, as the argument in this case has seemed to imply, that the Commission may have had to contemplate serious injury to the public interest because of its inability with very limited funds and staff to perform the enormous task of investigation and analysis imposed upon it in times when so many public utilities are submitting important proposals within its jurisdiction and the statutory scheme requires it to act promptly or let proposals go by default. But the remedy lies with Congress. If changes in the law are needed, or more personnel to administer existing law, or both, it is not for the administrative agency or the courts to try to make up for this deficiency by taking unauthorized short cuts or indulging time saving procedures which fail to accord parties the rights which the law as written gives them. Viewed in most favorable light, that seems to us to be what the Commission has tried to do here. It follows that the order of May 29 must be set aside as wholly beyond the authority of the Commission." *Mississippi River Fuel Corp.* v. *Federal Power Com'n*, 202 F.2d 899, 902-903 (1953), appeal dismissed, 345 U.S. 988.

It is not our position that a denial of a hearing, either under a rule or in an individual case, if a hearing is not required by statute, is unrelated to "a vast proliferation of hearings" by which the processes of regulation would be "prolonged" or "crippled". *FPC* v. *Texaco, Inc.*, 377 U.S. 33, 44, (1964). We say only that where the statute mandates a hearing it may not be denied in an individual case on the ground that administrative inconvenience or even such "a vast proliferation" will occur.

In the new drug situation with which we are dealing there is before the court only the unsubstantiated statement of the Government that such a vast proliferation would ensue. It is our contention (See Point I) that HW&D has submitted evidence to FDA which raises a substantial and material issue of fact and that, as the Fourth Circuit thought, a hearing is required to determine whether there is, in fact, substantial evidence of the effectiveness of Lutrexin. This evidence, we submit, even brings the case within the regulation upon which the Government relies to deny a hearing.

B. The Burden of Proof in Withdrawal Proceedings

The Government refers to *Ubiotica Corporation* v. *Food & Drug Administration*, 427 F.2d 376, 378 (6th Cir. 1970), which held that, by Section 505 of the Act the Congress clearly placed upon the applicant for an NDA the burden of showing that the drug which it proposes to distribute in interstate commerce is both safe and effective for its intended use.

But that is not the situation here. Here there is an attempt to place the burden of proof, not upon an *applicant* for an NDA, but upon one whose NDA became effective in 1953, the alleged approval of which FDA seeks to withdraw.[24]

It is significant, moreover, and the Court observed in *Ubiotica*, that "the Government came forward with proof as to why petitioner had not satisfied the burden of proof required of a new drug applicant under Section 355"

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[24] We maintain in our Brief in No. 72-414 that, the NDA for Lutrexin was not "deemed approved" under Section 107(c)(2) of the Drug Amendments and is, therefore, not subject to withdrawal of approval proceedings. Obviously it was not actually approved because approval of NDA's was not instituted until the enactment of the 1962 Amendments.

(427 F.2d at 378). It even introduced a "double-blind" study to show the ineffectiveness of the drugs in question. The hearing, affording cross-examination of Government witnesses, and the evidence introduced in that case, as shown by the Court's opinion, stand in sharp contrast to the summary treatment which FDA has given the studies by eminent specialists in the Lutrexin matter.

The structure of Section 505(e), providing for withdrawal of approval of NDAs, clearly contemplates that the burden of showing compliance with the statutory conditions for revocation is upon FDA.

One of the grounds of withdrawal is new evidence that the drug is not safe (Section 505(e)(2)). Surely the Commissioner may not make the finding required without producing such new evidence as the basis for the required finding. Under Section 505(e)(4) approval of an application may be withdrawn if the Commissioner finds "that the application contains any untrue statement of a material fact." It seems inconceivable that approval of an application could be withdrawn on this ground without the production by the Commissioner of the evidence that the applicant's statement was untrue. Likewise, under Section 505(e)(3) approval of an NDA may be withdrawn "on the basis of new information before [the Commissioner] with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have . . ." The only way to show that the evidence submitted by HW&D on Lutrexin is not substantial is for FDA to introduce countervailing evidence.

These and each of the several other bases for withdrawal of approval of NDA's are also conditioned upon

"due notice and opportunity for a hearing to the applicant." We have already noted that the statute itself and its legislative history contemplate an actual hearing (except, of course, where there is no fact question involved).

It seems clear, therefore, that the application of the May, 1970 regulations in such a manner as to shift the burden of proof from FDA to HW&D flouts the statutory mandate.

The proponent of an order approving an NDA is the applicant. The proponent of an order withdrawing approval is the Commissioner. In the latter situation Section 7(c) of the Administrative Procedure Act provides (5 U.S.C. 556(d)) that:

> "Except as otherwise provided by statute, the proponent of a rule or order has the burden of proof."

Since the Food, Drug and Cosmetic Act does not otherwise provide, Section 7(c) is applicable and it is evident that by reason of that Section alone, the burden is on the Commissioner in a withdrawal of approval proceeding.

This means, according to the Court of Appeals of the District of Columbia that it was incumbent upon the Commissioner "to state facts and reasons showing at least prima facie that the evidence before him raised no material issue of fact which would justify a hearing" (*USV Pharmaceutical Corporation* v. *Secretary of Health, Education & Welfare*, 466 F.2d at 461).

". . . It is the general rule that . . . 'the burden of proof lies upon him who affirms, not him who denies' ". *National Motor Freight Traffic Association, Inc.* v. *United States*, 242 F. Supp. 601, 605 (D.D.C. 1965).

C. FDA's "Summary Judgment" Regulations Viewed in the Light of the Structure of Section 505.

FDA relies on decisions in the sixth and second circuits[25] and on a decision in the district court in the third circuit[26] to support the validity of its hearing procedures. For the reasons set forth below, we submit that those courts erred and their decisions should not be followed by this court.

The review provisions of Section 505, 21 USC 355, are so structured as to make it clear that Congress intended a hearing on proposals to withdraw NDAs if the applicant requests a hearing. Thus, Section 505(e), 21 USC 355(e), provides: "The Secretary shall, after due notice and opportunity for a hearing" withdraw approval of an NDA if he makes the requisite statutory findings. The appeal provision (Section 505(h), 21 USC 355(h)) states that "The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive", and that, upon a proper showing, the reviewing court may grant a request "for leave to adduce additional evidence" before the agency:

> "The court may order such additional evidence to be taken by the Secretary and to be adduced *upon the hearing* in such manner . . . as to the court may seem proper" (Emphasis supplied).

A reading of these provisions leads one ineluctably to the conclusion that Congress deliberately intended to require an evidentiary hearing prior to withdrawal of an NDA. If this were not the case, the use of the terms quoted above would be meaningless. That this is so is apparent in the case at bar. Thus, there is not "substantial evidence" upon which the finding of the Secre-

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[25] *Upjohn Company* v. *Finch*, 422 F.2d 944 (6th Cir. 1970); *Pfizer, Inc.* v. *Richardson*, 434 F.2d 536 (2d Cir. 1970).

[26] *Pharmaceutical Manufacturers Association* v. *Richardson*, 318 F. Supp. 301 (D. Del. 1970).

tary can be based, for no such evidence was adduced at a hearing, and therefore, the findings of FDA in this case can hardly be considered conclusive. Similarly, the phrases in Section 505(h) "adduce additional evidence" and "order such additional evidence be taken" and "to be adduced" make little sense in a case before the appellate court based upon an order entered without a hearing.[27]

The opinions in *Upjohn*, *Pfizer*, and *Pharmaceutical Manufacturers Association*, *supra*, did not analyze the framework of Section 505 in upholding FDA's regulations. For this reason alone, this court should not follow those decisions.

A proffer of evidence of the caliber described in Point I, *supra*, is a sufficient showing that a hearing is warranted in this case. Contrary to FDA's position, Congress clearly intended that a hearing be held under these circumstances. As we show in the Argument, *supra*, under Background, FDA thought so too as late as the latter part of October, 1969.

D. Additional Contentions of the Government

The Government states that "the Court of Appeals did not find that any of the Commissioner's conclusions were unreasonable, erroneous, or arbitrary, but simply ordered a hearing because something might come out at such a hearing that would show that the studies were not as defective as they appeared to be on their face" (Br. 13). On the contrary, the Court's discussion of the Commissioner's action clearly reflected its view that the action was arbitrary and unreasonable. Moreover, the

[27] Where only a question of legal interpretation is involved, the Court of Appeals would not be dependent upon findings supported by substantial evidence and could, therefore, render a decision.

Court concluded that the objections raised by the Commissioner "do not justify a final conclusion, made *ex parte*, without a hearing, that it 'clearly appears' that there is no genuine issue of fact on the effectiveness of Lutrexin; . . . at most, they merely create a genuine issue of fact to be resolved at a hearing upon proper evidence" (J.A. 180).

As it did in its petition for a writ of certiorari, the Government again cites *United States* v. *Storer Broadcasting Company*, 351 U.S. 192 (1956) and *Federal Power Commission* v. *Texaco*, 377 U.S. 33 (1964) in support of its argument that the May 8, 1970 regulations, as applied to deny HW&D a hearing, are valid rules. (Br. 22-23). But, as we pointed out in our brief in opposition to the petition, in those cases there was no factual issue upon which to hold a hearing. It was either conceded or obvious that the applications to the agencies failed to conform to the rules involved. That is certainly not true here, as the Fourth Circuit held.

The Government states that "the Courts of Appeals have similarly declined to insist upon the holding of hearings when there are no material issues of fact to be resolved," citing cases (Br. 23). We hope we have made it clear that we interpret the opinion of the Court of Appeals as holding that issues of material fact have, indeed, been raised by the evidence presented to FDA by HW&D. It is our position, as it was the position of the Court of Appeals, that the Commissioner has construed the definition of substantial evidence in Section 505 in too narrow a manner.

The Government states:

> "Nearly 6,000 of the 16,500 claims evaluated by NAS-NRC received 'possibly effective' ratings (see n. 13, *supra*, and accompanying text), and if such a rating entitles the manufacturer to an evidentiary

hearing, FDA would be obliged to hold hearings on thousands of claims with respect to which the manufacturer had not produced any evidence meeting the requirement of law." (Br. 29).[28]

Neither the Court of Appeals nor HW&D has stated that a "possibly effective" rating by an NAS-NRC panel constitutes substantial evidence of effectiveness or requires the holding of a hearing. We maintain only that the evidence submitted by HW&D is of such stature as to require a hearing on the question of whether there is substantial evidence of effectiveness of Lutrexin, particularly since FDA has failed to meet its burden of presenting facts to the contrary. FDA knows very well that not many of the 6,000 claims evaluated as "possibly effective" are supported by the kind of evidence submitted by HW&D and that many of the manufacturers making such claims did not bother to request a hearing, even at a time when FDA itself believed that it was obligated to grant the hearing. Yet the Government, in its zeal to denigrate the studies by eminent specialists, submitted by HW&D, has even gone to the extreme of labeling them "anecdotal" (Br. 30).

We show in Part I that the affidavits and medical studies submitted by HW&D cannot rationally be described as an "heterogeneous and unorganized mass of documents." Nor can they, as we have shown, be dismissed as being "testimonial" or "anecdotal" in nature. It is true that HW&D had also submitted a substantial number of letters from practicing physicians requesting the agency to permit them to continue to use Lutrexin in their obstetrical practice. These letters do not detract from the medical studies and affidavits submitted by HW&D. They merely indicate that the doctors took time

[28] The reference here is to *claims* as distinguished from products each of which may have more than one claimed use. See Point III, *supra* at 33.

out from their busy practices to inform FDA that the drug was needed to prevent tragic infant deaths due to premature birth.

With respect to the determination of FDA that Pfizer, Inc. was not entitled to a hearing, Judge Friendly is quoted as saying that ". . . such a determination is peculiarly within the FDA's expertise and we should be reluctant to intrude in medical matters we do not truly understand . . ." (Br. 34). But Judge Friendly also said, in the same sentence ". . . it is apparent even to us laymen that the FDA had a reasonable basis for considering that Pfizer's submissions did not comply with the requirement of the statute and the regulation" 434 F.2d at 547. The Court below did not think this was true of HW&D's submissions and we believe our analysis of them shows that the court was right.

We have already pointed out that there is no justification for the Government's construction of the Fourth Circuit's opinion to mean that the Commissioner must "negative the almost endless, if remote, possibilities that a hearing might still turn up relevant evidence" (Br. 35). The Court clearly held that HW&D's evidence and the Commissioner's analysis of them created a "genuine question of fact to be resolved at a hearing" (J.A. 180).

HW&D did not, as the Government points out (Br. 38), seek a waiver of the requirements of the regulations. The reasons were that HW&D considered the regulations invalid and that, even under the regulations it was entitled to a hearing (see Points II and III). We would not expect a waiver to be granted if it were requested since FDA has maintained throughout this proceeding that Lutrexin is not effective. It is somewhat disingenuous to imply, even indirectly, that the result might have been otherwise.

IV

RESPONDENT HW&D IS ENTITLED TO A HEARING UNDER REGULATIONS IN EFFECT WHEN THE COMPANY ELECTED TO ACCEPT THE OPPORTUNITY FOR A HEARING PROFFERED IT BY FDA.

An opportunity for a hearing was offered HW&D by the Commissioner on March 22, 1969 (J.A. 12). HW&D made a timely election to avail itself of the opportunity for a hearing (J.A. 14). FDA's regulations in effect at the time provided:

> "If the applicant elects to accept the opportunity for a hearing by written request within 30 days after such notice, a hearing examiner will be named and he shall issue a written notice of the time and place at which the hearing shall commence, not more than 90 days after the expiration of such 30 days unless the hearing examiner and the applicant otherwise agree" (21 CFR 130.14(b), revised as of January 1, 1969).

It is apparant from the review of FDA's subsequent actions set forth in the Argument, *supra*, under "Background", that FDA failed to follow its own rules when it denied HW&D a hearing and applied retroactively the "summary judgment" regulations.

By failing to follow its own rules FDA deprived HW&D of due process of law and prejudiced the company's rights. *United States* v. *Leahey*, 434 F.2d 7 (1st Cir. 1970); *Hammond* v. *Lenfest*, 398 F.2d 705 (2d Cir. 1968); *Pacific Molasses Co.* v. *FTC*, 356 F.2d 386 (5th Cir. 1966); *Sangamon Valley Television Corp.* v. *United States*, 269 F.2d 221, 224 (D.C. Cir. 1959); *Bucks County Cable TV, Inc.* v. *United States*, 299 F. Supp. 1325 (D. Pa. 1969). The rule was applied in *United States* v. *Heffner*, 420 F.2d 809 (4th Cir. 1969) because of failure

of the Internal Revenue Service to follow its rules relating to warnings by investigators to persons who are suspected of tax fraud, and in *United States ex rel. Brooks* v. *Clifford*, 409 F.2d 700, 706 (4th Cir. 1969), rehearing denied, 412 F.2d 1137 (1969), where the Department of Defense did not follow its procedures for discharge of conscientious objectors from the Army.

In *Elmo Division of Drive-X-Company, Inc.* v. *Dixon*, 348 F.2d 342 (D.C. Cir. 1965), the Federal Trade Commission and appellant's predecessor in interest entered into a consent settlement providing that the settlement could be set aside as provided in Rule V(f) of the Commission's Rules of Practice. Under that rule, if the settlement was reopened and set aside the Commission could *thereafter* undertake corrective action by adversary proceedings as to any acts or practices not prohibited by the settlement. It was alleged that the Commission side-stepped the reopening procedures and issued a new complaint which would result in a second trial upon the same charges. The court held that the Commission was required to abide by its own rule and that "the incorporation of [Rule V(f)] into the consent order 'vested' appellant with the right of a reopening hearing". 348 F.2d at 346.

Here, FDA effectively incorporated in its notice of opportunity for a hearing its rule that a hearing would be held upon acceptance of the proffered opportunity. In any event the rule itself was clearly complied with by petitioner and petitioner was thus "vested" with the right of a hearing.

In *Greene* v. *United States*, 376 U.S. 149 (1964) petitioner claimed compensation for loss of earnings resulting from a discharge from employment with a government contractor, because of a revocation of security clearance, which the courts had held was unlawful and

void. A 1955 regulation of the Department of Defense provided for such compensation. While the claim was being processed a new regulation was adopted, in 1960, placing severe conditions on the granting of compensation, which petitioner could not meet.[29] His claim was processed under the new regulation and denied. The court said—

> "Whatever petitioner's rights are, there can be no doubt that they matured and were asserted under the 1955 directive" (376 U.S. at 160).

> "In summary then, we hold that petitioner was entitled as a matter of right to compensation under the 1955 regulation and that, when the Department of Defense rejected his claim, he was not required to proceed administratively under the 1960 regulations . . ." (376 U.S. at 164-165).

See also *Service* v. *Dulles*, 354 U.S. 363 (1957) and *Vitarelli* v. *Seaton*, 359 U.S. 535 (1959).

It is apparent that for reasons of convenience and expediency, FDA has altered its policy of granting hearings under Section 505 to the prejudice of HW&D whose right to a hearing had matured under prior FDA policy. This is not proper agency action. *Upjohn Company* v. *Pennsylvania Railroad Company*, 381 F.2d 4 (6th Cir. 1967). There the Court said:

> "The Commission's only basis for reversal of its prior decision is that after some three years of elapsed time in a proceeding in another matter with the same fact situation, it has adopted a different policy, and therefore seeks to apply retroactively its new policy" (381 F.2d at 5).

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[29] We have shown that HW&D's submissions to FDA do meet the conditions prescribed by the Agency's regulations.

CONCLUSION

For the foregoing reasons, the judgment of the Court of Appeals should be affirmed.

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In the Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-414

HYNSON, WESTCOTT & DUNNING, INCORPORATED,
CROSS-PETITIONER

v.

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

BRIEF FOR THE RESPONDENTS

OPINIONS BELOW

The opinion of the court of appeals (J.A. 173–180) is reported at 461 F.2d 215. The order of the Commissioner of Food and Drugs was published in the Federal Register on June 18, 1971 (J.A. 72–78; 36 Fed. Reg. 11763).

JURISDICTION

The judgment of the court of appeals (J.A. 181) was entered on May 24, 1972. The petition for a writ of certiorari was filed, pursuant to an extension of

time granted by Mr. Justice Rehnquist, on September 11, 1972. On January 8, 1973, this Court granted the petition and consolidated the case with four other cases in which it also granted writs of certiorari.[1] The jurisdiction of this Court rests on 28 U.S.C. 1254(1) and 21 U.S.C. 355(h).

QUESTIONS PRESENTED

1. Whether, in a proceeding under Section 505(e) of the Federal Food, Drug, and Cosmetic Act to withdraw approval of a new drug application, the Commission of Food and Drugs has authority to determine initially whether the drug involved is a "new drug" within the meaning of Section 201(p) of the Act.

2. Whether a drug may be held not to be a "new drug" under Section 201(p)—that is, to be generally recognized among qualified experts as safe and effective for its intended use—in the absence of published adequate and well-controlled investigations of the type defined by Section 505(d) of the Act and the Commissioner's regulations.

3. Whether a drug for which a new drug application was on file with the Food and Drug Administration at the time of enactment of the Drug Amendments of 1962, which was at that time no longer a "new drug" under the definition contained in the 1938 Act, is exempted from the drug effectiveness requirements of the 1962 Amendments by Section 107(c)(4)

[1] The other cases are *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, No. 72–394, *CIBA Corporation* v. *Weinberger*, No. 72–528; *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72–555; and *USV Pharmaceutical Corporation* v. *Weinberger*, No. 72–666.

thereof (and whether the application for such drug was not "effective" within the meaning of Section 107(c)(2) of the 1962 Amendments, so that approval of the application could not be withdrawn by the Food and Drug Administration).

STATUTORY PROVISIONS AND REGULATIONS INVOLVED

Section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p), J.A. 475) provides:

> The term "new drug" means—
>
> (1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or
>
> (2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

Section 107(c)(2) of the Drug Amendments of 1962, 76 Stat. 788, Note following 21 U.S.C. 321 (1970 ed.) (J.A. 481), provides:

> An application filed pursuant to section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

Section 107(c)(4) of the Drug Amendments of 1962, 76 Stat. 789, Note following 21 U.S.C. 321 (1970 ed.) (J.A. 482), provides:

> In the case of any drug which, on the first day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

Other pertinent provisions of statutes and regulations are set forth at J.A. 475–491.

STATEMENT

This is a cross-petition to review the same decision of the court of appeals from which the government has petitioned in *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, No. 72–394. We respectfully refer the

Court to our brief in No. 72–394 (pp. 3–10) for a full statement of the case, and we recite here only the facts relevant to the issues addressed in this brief.

On October 16, 1970, a month after it lost its district court suit against the Commissioner for declaratory relief (J.A. 23–24), Hynson renewed its request for an administrative hearing (J.A. 24). Hynson asked the Commissioner to decide: (1) whether Lutrexin was, because of alleged current general recognition by experts of safety and effectiveness, not a "new drug" within the meaning of Section 201(p) of the Act; and (2) whether Lutrexin was, because of alleged general recognition of safety on October 9, 1962, "grandfathered" under Section 107(c)(4) of the 1962 Drug Amendments (J.A. 26).[2] In support of its request for a hearing on these issues, Hynson submitted certain affidavits of physicians and reports of medical studies which it had presented to the district court in its unsuccessful suit (J.A. 30–72, 87–121, 131–135).

On May 31, 1971, the Commissioner issued an order denying Hynson's request for a hearing and withdrawing approval of the new drug application ("NDA") for Lutrexin (J.A. 72–78). The Commissioner held that Lutrexin was not exempt under Section 107(c)(4) because the drug's NDA, which had become effective in 1953, had not been withdrawn prior to the enactment date of the 1962 Amendments, and thus the drug was

[2] Hynson also asked the Commissioner to determine whether under Section 505 of the Act there was substantial evidence of Lutrexin's effectiveness (J.A. 26).

"covered by an effective application" within the meaning of Section 107(c)(4)(C) (J.A. 74).[3] The Commissioner also ruled that Lutrexin was currently a new drug because there was no general recognition among experts of its effectiveness. The basis for this ruling was that Hynson had failed to present evidence of adequate and well-controlled clinical investigations in support of the drug's efficacy. In a detailed review of Hynson's documentation, the Commissioner demonstrated how each study showed deficiencies on its face which prevented it from being regarded as an adequate and well-controlled study (J.A. 74–78). He concluded, accordingly, that "there is no data base upon which experts can fairly and responsibly conclude that the safety and effectiveness of the drugs has been proven and is so well established that the drugs can be generally recognized among such experts as safe and effective for their intended uses" (J.A. 74).[4]

On petition for review, the court of appeals affirmed the Commissioner's ruling that Lutrexin is not exempt under Section 107(c)(4), although it held that the issue should have been decided by the district court and not by the Commissioner (J.A. 176–177). The

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[3] The Commissioner did not take issue with Hynson's contention that on October 9, 1962, Lutrexin was generally recognized as safe by experts, that is, was not a new drug, and we assume for the purposes of this brief, therefore, that on that date Lutrexin was not a new drug as defined by the 1938 Act.

[4] The Commissioner also ruled that Hynson was not entitled to a hearing on the question of substantial evidence of effectiveness because it had failed to present adequate and well-controlled clinical investigations in support of its claim that substantial evidence of effectiveness exists (J.A. 78).

court neither affirmed nor rejected the Commissioner's holding that Lutrexin was currently a new drug.[5]

ARGUMENT

I. INTRODUCTION AND SUMMARY

The court of appeals implicitly held in this case that only the district court had authority initially to determine whether Lutrexin is a new drug (J.A. 176–177).[6] Hynson contends that the Commissioner has authority to determine new drug status in proceedings to withdraw approval of the product's new drug application ("NDA") under Section 505(e) of the Act (Br. 15–20). We agree. Since we have treated this issue at length in our briefs in *CIBA* (No. 72–528) and *Bentex* (No. 72–555), and since we do not disagree with the arguments advanced by Hynson on this point, we shall not discuss the issue further here.

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[5] The court reversed the Commissioner's withdrawal of approval of the NDA for Lutrexin for failure to provide an opportunity for hearing on the question whether Hynson had presented substantial evidence of the drug's effectiveness (J.A. 181). The correctness of the court's ruling on this point is at issue in No. 72–394.

[6] The court explicitly held only that Hynson's claim for an exemption under Section 107(c)(4) was for the district court and not the Commissioner to decide (J.A. 176–177). However, since Section 107(c)(4) provides exemption from the definition of new drug contained in Section 201(p), and since in both its *Bentex* and *USV* opinions the court held that the district courts alone may decide whether a drug is a new drug (J.A. 266–267, 467), there is no doubt that the court here too meant that the Commissioner is without authority to decide whether Lutrexin is a new drug. We contend (see point II, *infra*) that the Commissioner correctly ruled that Lutrexin is a new drug, and we believe the court of appeals should have affirmed that ruling.

For the reasons stated in points II and III, *infra*, we do not believe that the existence of such jurisdiction aids Hynson in the present case, since it becomes pertinent only if this Court disagrees with the Commissioner's reasons for rejecting these claims. Hynson contends (1) that it is entitled to establish general recognition of safety and effectiveness under Section 201(p) by means of evidence that would not suffice to satisfy the requirements of Section 505 for approval of an NDA; and (2) that it can establish entitlement to exemption, pursuant to Section 107(c)(4), from the drug effectiveness requirements added to Sections 201(p) and 505 by the 1962 Amendments by demonstrating that on October 9, 1962, its product was no longer a "new drug" under the pre-Amendments definition.[7] If, contrary to our position, either of these contentions is accepted, we would agree that the Commissioner's action withdrawing approval of Lutrexin's NDA was based on erroneous premises, and that the matter should be remanded to the agency for further consideration—and that Hynson is entitled to a hearing before the agency on its claim for exemption, provided it can show that it has evidence that would support its claim under the standard established by the Court.

We show in point II, *infra*, that if there is a lack of substantial evidence of Lutrexin's effectiveness, so that approval of its NDA must be withdrawn pursuant to Section 505(e), that determination also serves

[7] Hynson's arguments in support of its right to a hearing on these issues (Br. 28–38) depend, of course, on acceptance of these contentions.

to foreclose the possibility that Lutrexin is "generally recognized" by qualified experts as effective. In adopting the requirement in the 1962 Amendments that drug effectiveness claims be supported by evidence consisting of "adequate and well-controlled investigations, including clinical investigations * * *," Congress heeded the unanimous testimony of a number of the Nation's leading clinical pharmacologists and medical educators that only such investigations, and not the clinical impressions of practicing physicians or poorly controlled studies, can provide a scientifically sound basis for the drug effectiveness inquiry. At the same time that Congress was amending Section 505 to incorporate the requirement of modern, scientific standards of drug efficacy evaluation, it also amended Section 201(p) to expand the definition of "new drug" to include drugs not generally recognized by experts as effective. Surely Congress did not intend to permit drugs to remain on the market, in the absence of adequate and well-controlled investigations supporting their efficacy claims, on the basis of "expert" opinions rooted in the very kind of unscientific evidence Congress rejected in Section 505.

The structure of the Act, in its normal application, confirms that the requirements of "general recognition" and material use contained in Section 201(p), which must be met in order for a drug not to be "new," are additional to the safety and effectiveness showing that must be made under Section 505. This is because there is no way for a drug to achieve general recognition and material use unless it has in fact

been widely written about and used; since distribution of the drug without an approved application is illegal, it follows that the drug must be able to satisfy the standards of Section 505 to obtain the approved application that will permit it ultimately to achieve "not new" status.

Lutrexin and other similarly situated drugs have escaped this normal situation because they were first marketed at a time when effectiveness was not a criterion under either Section 201(p) or Section 505. Nevertheless, it is clear that Congress intended such drugs, if not grandfathered under the 1938 Act or exempted by Section 107(c)(4) of the 1962 Amendments, to be subject to review for effectiveness and removal from the market for failure to satisfy the "substantial evidence" standards of Section 505. Congress specifically provided in Section 107(c)(3)(B) that applications with respect to drugs then on the market would, after a two-year grace period, be subject to withdrawal of approval under Section 505(e)(3). That provision specifies that approval shall be withdrawn if there is a lack of "substantial evidence" of effectiveness, which, of course, turns upon the existence of adequate and well-controlled investigations. Where it has been validly determined in administrative proceedings, in accordance with this congressional scheme, that there is a lack of substantial evidence of a drug's effectiveness, Congress surely did not intend to permit such a determination to be mooted by reliance upon insubstantial evidence of effectiveness, *i.e.,* opinions predicated on scientifically unreliable bases.

Hynson contends, alternatively, that Lutrexin is exempted from efficacy regulation by Section 107(c)(4) because it was, on the day preceding enactment of the 1962 Amendments, not a "new drug" under the safety-only standards then prevailing. It argues that, not being a new drug, its product was no longer subject to regulation under Section 505 and its application was therefore no longer "effective" within the meaning of Clause (C) of Section 107(c)(4). By thus linking the concept of an effective application to new drug status, however, Hynson would render Clause (C) wholly superfluous, since the requirements for exemption would be met by a drug satisfying Clauses (A) and (B). The construction adopted by the court of appeals, which recognizes that an application that had become effective prior to 1962 remained "effective" for purposes of Section 107(c)(4) (unless suspended by FDA) regardless of the subsequent history of the drug, gives a reasonable meaning to the provision and comports with the basic thrust of the 1962 Amendments to remove ineffective drugs from the market. That construction also comports with the unequivocal and repeated statements in the committee reports and the debates that the exemption in Section 107(c)(4) was intended to relate to drugs that had *never* been subject to new drug regulation under the pre-1962 standards—a condition Lutrexin obviously cannot satisfy.

The history of the enactment of the 1962 Amendments confirms the congressional intent to make drugs subject to re-evaluation on effectiveness grounds even

though they were not "new drugs" under the pre-1962 standard. The bill, as originally reported by the Senate Committee in July, 1962, would have exempted such drugs, but this initial proposal was significantly revised and tightened after the thalidomide tragedy, including the adoption of transitional provisions in Section 107(c) specifically providing for efficacy review of pre-1962 drugs, with the limited exception carved out by Section 107(c)(4). Under Hynson's interpretation, however, that exception would apply to nearly all drugs then on the market, while the regulatory provisions adopted by Congress would apply only to the relatively small group which, although approved on safety grounds by FDA, were not yet generally recognized as safe. There is no warrant for such a construction, which would almost entirely defeat the regulatory thrust of the transitional provisions.

Finally, it is clear from the structure of the original Act that applications in fact remained "effective" in a significant sense (although perhaps inactive) even after a drug had ceased to be "new." This is because Section 505(e) directed suspension of the effectiveness of an application in the event new information came to light questioning the drug's safety.

II. THE EXISTENCE OF PUBLISHED ADEQUATE AND WELL-CONTROLLED CLINICAL INVESTIGATIONS IS A PREREQUISITE TO A FINDING UNDER SECTION 201(p) OF GENERAL RECOGNITION OF A DRUG'S EFFECTIVENESS

The Commissioner ruled that Lutrexin is a "new drug" as defined in Section 201(p) of the Act. He stated (J.A. 74):

> No adequate and well-controlled clinical investigations published in the medical literature have been identified. Therefore, there is no data base upon which experts can fairly and responsibly conclude that the safety and effectiveness of the drugs has been proven and is so well established that the drugs can be generally recognized among such experts as safe and effective for their intended uses.

Hynson contends that the Commissioner applied the wrong standard to the "new drug" inquiry. While it concedes that the existence of adequate and well-controlled clinicial investigations is essential to a finding of a new drug's effectiveness under Section 505, it nonetheless argues that status as a "new drug" under Section 201(p), which turns upon "general recognition" among qualified experts of a drug's effectiveness, does not require the existence and publication of scientifically valid evidence of effectiveness (Br. 21–27). Our view, on the other hand, is that the statutory scheme and the history underlying the adoption by Congress of scientific criteria for evaluation of drug effectiveness show that Congress acted on the premise that "experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs," whose collective judgment is the subject of the Section 201(p) inquiry, would necessarily predicate that judgment on the kind of evidence—or lack of it—required by Section 505; by the same token, the scientific community would necessarily reject, as a basis for general recognition of effectiveness, the kind of uncontrolled clinical impressions upon

which Hynson seeks to rely, unless corroborated by adequate and well-controlled clinical investigations.

Section 201(p) defines the term "new drug" for purposes of the Act. Under this definition, a drug is a "new drug" unless (1) it is generally recognized among qualified experts as safe and effective for its intended use, *and* (2) it has been so used to a material extent or for a material time (see Section 201(p)(1) and 201(p)(2) at J.A. 475). The Act, however, nowhere specifically defines what constitutes general recognition among qualified experts. Therefore, in order to give content to that term, and thus to the definition of "new drug," it is appropriate to look to the purposes to be achieved by the Act, as reflected in the related provisions of the Act and in its legislative history. Cf. *United States* v. *Bacto-Unidisk*, 394 U.S. 784.

In our view, the most pertinent related provision of the 1962 Amendments is the definition of "substantial evidence" of effectiveness in Section 505(d). Our contention, in essence, is that the general recognition among qualified experts to which Congress referred in Section 201(p) should be interpreted harmoniously with the definition of "substantial evidence" adopted by Congress in Section 505(d), and thus should not be construed to include any concept of "recognition" based on less than "substantial evidence" of effectiveness. Hynson contends the contrary. Our position on this issue is, we submit, more consistent both with the legislative history of the 1962 Amendments and with the overriding purpose of the

Amendments to insure that drugs allowed upon the market are effective for their claimed uses as well as safe. Cf. *United States* v. *Bacto-Unidisk, supra,* 394 U.S. at 798; *United States* v. *Sullivan,* 332 U.S. 689, 693–695; *United States* v. *Dotterweich,* 320 U.S. 277, 280.

A. THE HISTORY OF THE 1962 DRUG AMENDMENTS SHOWS THAT CONGRESS WAS PERSUADED THAT ONLY ADEQUATE AND WELL-CONTROLLED CLINICAL INVESTIGATIONS COULD PROVIDE A SCIENTIFICALLY RELIABLE BASIS FOR EVALUATION OF DRUG EFFECTIVENESS CLAIMS

The history of the Drug Amendments of 1962 leaves no doubt that Congress intended a rigorous pre-marketing examination of drugs to assure that a substantial scientific basis exists for their claims of effectiveness, and that it further intended that, even after approval and marketing, drugs would continue to be under supervision for safety and effectiveness thereafter, in light of evolving medical knowledge, so that products disclosed by new data to be unsafe or ineffective would not remain on the market. The system of pre-marketing clearance and post-marketing supervision by the expert administrative agency was the primary means established for exclusion of ineffective products from the market.

In Section 505(d), as amended in 1962, Congress adopted a definition of the kind of evidence to be considered "substantial evidence" of drug effectiveness claims. That definition reflects modern, scientific concepts of pharmacology. The kind of evidence required consists of "adequate and well-controlled investigations, including clinical investigations, by ex-

perts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have * * *'' (21 U.S.C. 355(d), J.A. 478–479).

This congressional insistence upon substantiation of drug efficacy claims by means of rigorous, scientific evidence of a kind and quality that would be acceptable to expert pharmacologists—rather than by reliance upon the clinical impressions of practicing physicians or the results of inadequately designed and poorly controlled experiments—was the product of careful study and of the presentation of uncontradicted testimony in congressional hearings by many of the Nation's leading experts on clinical pharmacology, by prominent medical educators, and by representatives of the drug industry itself.[8] Appendix A, pp. 1a–12a, *infra,* outlines the testimony on this subject presented at the congressional hearings.

The experts explained to Congress in detail the need for controlled clinical testing and the difference between the validity of such scientific procedures and the unreliability of clinical impressions of therapeutic effectiveness by individual practitioners. The testimony drew a sharp distinction between the expert qualified to evaluate the effectiveness of drugs—named in both Sections 201(p) and 505(d)—and the working physician who applies to individual patients

[8] Drug Industry Antitrust Act, Hearings before the Subcommittee on Antitrust and Monopoly, Senate Judiciary Committee, 87th Cong., 1st Sess, pursuant to S. Res. 52 on S. 1552.

contemporary medical knowledge developed by expert scientific research. As one leading pharmacologist testified, the "'average practicing physician—and I haved helped to train hundreds of them—just does not have the time, the facilities, the skill, nor the training to be an expert in the determination of drug efficacy.'"[9] This testimony was echoed by the other expert witnesses, who in substance agreed with the observation of one of their number that "[t]he history of medicine is, unhappily, replete with examples of useless drugs employed for years, decades or centuries, by countless physicians before a few properly conducted experiments proved the drugs to be without value."[10] Confirming this view, the Chairman of the Pharmaceutical Manufacturers Association emphasized that in determining effectiveness the key words are "'well-conducted clinical trials by competent clinicians.'"[11]

In addition, Congress was informed in detail of the meaning of an adequate and well-controlled study. Such a study is designed to eliminate subjective influence on the part of either the investigator or the subject; it is conducted on a comparative basis, with a sufficient number of subjects to minimize the influence of chance factors on results; it is of sufficient duration to permit all consequences of the drug's administration to be evaluated; and its results can be confirmed by other clinical investigators using similar

[9] App A, *infra*, p. 4a.
[10] *Id.* at 5a.
[11] *Id.* at 8a.

methods.[12] The views expressed by these witnesses to Congress represent the consensus of experts in the evaluation of drug effectiveness. The reasons for these rigorous scientific requirements are explained more fully in Appendix B, pp. 13a–47a, *infra*.

Thus, in Section 505(d) Congress rejected as unreliable determinations of drug effectiveness based upon clinical impressions or "majority vote" of practitioners,[13] and adopted instead the criterion of adequate and well-controlled clinical investigations. Hynson nevertheless contends that for purposes of Section 201(p) "a drug may have enjoyed such widespread use and therapeutic success that qualified experts could conclude that it is generally recognized as safe and effective, even if no studies of any kind existed in the medical literature" (Br. 27). Under this view, "experts qualified * * * to evaluate the * * * effectiveness of drugs" may be argued to have based a determination of effectiveness solely upon the clinical impressions of individual practitioners and the existence of scientifically inadequate and poorly controlled studies—the very criteria Congress rejected as scientifically unreliable by enacting Section 505(d).[14]

We submit, instead, that Section 201(p) should be construed harmoniously with Section 505(d) and the

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[12] *Id.* at 2a–3a.

[13] *Id.* at 12a.

[14] It is particularly significant for this purpose that Section 505(d)'s definition of "substantial evidence" is in terms also applicable to proceedings under Section 505(e) for the withdrawal of an NDA, which can of course occur after the kind of widespread use to which Hynson refers.

congressional judgment the latter provision represents, by interpreting "general recognition" of effectiveness to mean more than, rather than less than, "substantial evidence" of effectiveness. The logic of this interpretation becomes apparent when the application of the two provisions in the normal, entirely prospective operation of the 1962 Amendments is considered.

B. THE NORMAL OPERATION OF THE REGULATORY SCHEME EMBODIED IN THE ACT REQUIRES DRUGS TO SATISFY THE CRITERIA FOR NDA APPROVAL IN SECTION 505 BEFORE THEY CAN CEASE TO BE "NEW DRUGS" UNDER THE DEFINITION IN SECTION 201(p)

In the ordinary course of entirely prospective operation of the 1962 Amendments, a drug could not acquire the characteristics necessary to cease being a "new drug" as defined in Section 201(p) unless it has first satisfied the safety and effectiveness standards of Section 505. The terms of Section 201(p) preclude any other result, since the provision renders it impossible to cease being a new drug without being used—Section 201(p)(2) explicitly requires use "to a material extent or for a material time," in addition to general recognition of effectiveness, in order for a drug to cease being a "new drug" (J.A. 475).

Since loss of "new drug" status can thus occur only after use, and since distribution of a "new drug" is unlawful without an application approved pursuant to the standards of Section 505, which require the manufacturer to produce "substantial evidence" of effectiveness in the form of "adequate and well-controlled investigations," the Act is designed so that

drugs on the market, unless exempt, will have mustered the requisite scientifically reliable evidence of effectiveness long before they are in a position to drop out of active regulation by ceasing to be a "new drug."

The substantial evidence of effectiveness initially offered to the Commissioner to obtain a marketing authorization does not, of course, establish that the drug is generally recognized as effective. It reflects only the scientific conclusions of the particular experts who performed the investigations that the product is therapeutically useful and their expectation that their fellow experts will agree with their conclusions when the scientific basis for those conclusions is made known to them. Thus, "not new drug" status comes about after these studies, or subsequent studies of the same kind, are published in the medical literature and inform other experts qualified in evaluating drugs of the product's effectiveness. Such studies then form the basis for general recognition by the experts that the drug is effective for its claimed uses. Once the product attains a consensus of expert acceptance, plus the actual usage of the product for a material time or to a material extent required by Section 201(p)(2) (primarily to provide greater insurance of safety), it may be viewed as currently exempt from Section 505's requirements, although its "new drug" status may be revived if expert knowledge changes.[15]

It is thus apparent that the statutory scheme is designed to condition "not new drug" status on the ability to satisfy the safety and effectiveness criteria

[15] See our brief in *USV* (No. 72–666) at p. 48, n. 31.

of Section 505, plus the ingredients added by Section 201(p)—general recognition of that ability plus material use.[16] Hynson seeks to fashion a loophole in this statutory structure by virtue of the fact that Lutrexin came on the market at a time when Section 505 contained different (safety only) standards for pre-marketing clearance than prevail today. But it is clear from the applicability and purpose of the 1962 Amendments, as discussed immediately below, that Congress did not intend products such as Lutrexin to escape scientific evaluation of their effectiveness.

C. THE 1962 AMENDMENTS CLEARLY CONTEMPLATED THAT DRUGS THEN ON THE MARKET, IF NOT EXPRESSLY EXEMPTED, WOULD BE SUBJECT TO REMOVAL FROM THE MARKET FOR FAILURE TO SATISFY THE DRUG EFFECTIVENESS STANDARDS OF SECTION 505

As is apparent from the structure and legislative history of the 1962 Amendments (see our brief in *USV,* pp. 17–29), Congress decided to subject all pre-1962 drugs to efficacy regulation except those grandfathered under the 1938 Act[17] and those specifically exempted by Section 107(c)(4). We show in point III, *infra,* that Lutrexin is not entitled to any such exemption from efficacy regulation. Accordingly, Sec-

[16] This view is further corroborated by the very terms of Section 201(p)(2), which indicate that Congress contemplated that general recognition of effectiveness would occur "as a result of investigations" and that such recognition could occur in the absence of material use of the drug.

[17] The grandfather provision contained in Section 201(p)(1) covers drugs subject to the 1906 Act, provided their labeling remains unchanged. Developments in pharmacology in the last 35 years have resulted in vast changes in products and claims, so that this exemption is of diminishing importance.

tion 107(c)(3)(B) (J.A. 482) makes it clear that, following the two-year grace period, approval of Lutrexin's NDA was subject to withdrawal under "clause (3) of the first sentence of section 505(e) * * * as amended * * *." That clause specifically provides for withdrawal of approval if "there is a lack of substantial evidence" that the drug is effective for its claimed uses.

In short, assuming we are correct that neither Section 107(c)(2) nor Section 107(c)(4) exempts drugs such as Lutrexin from administrative review for efficacy, Congress deliberately specified that such drugs should be evaluated for effectiveness on the basis of the existence of adequate and well-controlled clinical investigations. It is hardly conceivable that Congress intended that, after the Commissioner had made such an evaluation in the manner and pursuant to the standards Congress established and had found a product wanting, that product should nevertheless be able to stay on the market by producing the kind of evidence Congress had rejected as unscientific. A construction of the Act permitting such a result would be unsound, for it would "* * * impute to Congress a purpose to paralyze with one hand what it sought to promote with the other." *Clark* v. *Uebersee Finanz-Korp.*, 332 U.S. 480, 489.

Since the Act is not simply "a collection of English words," but a "working instrument of government" whose purposes are to protect the lives and health of the people (*United States* v. *Dotterweich*, 320 U.S. 277, 280), the construction urged by Hynson, under which the scientific standards of evaluation of drug

effectiveness selected by Congress may be discarded in favor of outmoded and unreliable criteria, should be rejected. Nothing in the statute requires that it be construed to enable a drug that had been examined under the criteria Congress prescribed and found wanting to remain on the market,[18] and the very purpose of the Act indicates that such a construction should be avoided.

[18] Hynson cites (Br. 32–35) a number of cases for the proposition that the determination under Section 201(p) is different from the determination under Section 505. While we disagree with the reasoning in some of these decisions, their holdings are not contrary to the government's argument here. All of these cases were proceedings involving products with respect to which no marketing authorization was on file. Thus the agency had never made a formal determination, in a proceeding under Section 505, whether the product met the safety and effectiveness standards for approval of an application. Moreover, with one possible exception, the courts in these cases refused in the absence of published reports of adequate and well-controlled studies to hold that the products involved were exempt. The possible exception is *United States* v. *Article of Drug Labeled "Quick-O-ver"*, 274 F. Supp. 443 (D. Md.), in which the effectiveness of the individual ingredients involved for the uses claimed was substantiated in the scientific literature and the court did not discuss this issue in its opinion. A more recent decision, *United States* v. *An Article of Drug* * * * *Xerac*, CCH Food, Drugs, Cosmetic L. Rep. ¶ 40,836 (N.D. Ill.), accepted the views expressed in this brief. And other recent authorities recognize that lack of documented sources of information bars the widespread expert knowledge of the drug's effectiveness or safety necessary to achieve "not new drug" status under Section 201(p). See *e.g.*, *United States* v. *An Art. of Drug* * * * *"Bentex Ulcerine"*, 469 F. 2d 875 (C.A. 5), petition for a writ of certiorari pending, No. 72–1198; *United States* v. *41 cases, more or less*, 420 F. 2d 1126, 1130– (C.A. 5); *United States* v. *Article of Drug (Norwich Pharmacal)*, 415 F. 2d 390 (C.A. 5), affirming, 294 F. Supp. 1307 (N.D. Ga.); *United States* v. *Article of Drug* * * * *"Mykocert"*, 345 F. Supp. 571, 574 (N.D. Ill.).

III. SECTION 107(c) OF THE 1962 AMENDMENTS DOES NOT EXEMPT LUTREXIN FROM WITHDRAWAL OF APPROVAL OF ITS NDA ON GROUNDS OF FAILURE TO ESTABLISH EFFECTIVENESS

Petitioner contends that Sections 107(c)(2) and 107(c)(4) of the 1962 Amendments exempt it from withdrawal of approval of its NDA on effectiveness grounds. This contention is predicated solely on the fact—which we concede *arguendo* for purposes of this case—that Lutrexin was no longer a "new drug" on October 9, 1962, because it was "generally recognized" as safe at that time. Petitioner reasons that, therefore, its NDA, which had become effective in 1953, had ceased to be "effective" by 1962, since at that time an NDA was no longer required for the marketing of drugs containing lututrin to be used as prescribed in Lutrexin's labeling.

We submit that the court of appeals was correct in rejecting this argument and in holding that an application that had become effective before October 10, 1962, remained "effective" for purposes of Section 107(c) regardless of the subsequent history of the drug (with the limited exception, not here relevant, of NDAs whose effectiveness had been suspended by FDA under old Section 505(e)[19]). This

[19] Petitioner suggests that this limited exception to the continuing effectiveness of an NDA leads to a "bizarre result" contrary to the purpose of Section 505(e) to prevent further distribution of unsafe or ineffective drugs (Br. 42–43). (See also USV's brief in No. 72–666, at p. 71.) Of course, the fact that the effectiveness of an NDA had been suspended by FDA for safety reasons would hardly qualify the product for Section 107(c)(4)'s exemption from efficacy regulation, since

conclusion is required both by the structure of the statute and by the clear congressional explanation of its intended operation.

A. LUTREXIN IS NOT ENTITLED TO EXEMPTION UNDER SECTION 107(C)(4)

Petitioner contends that Lutrexin is exempt under Section 107(c)(4) from the effectiveness requirements of the 1962 Amendments (Br. 41–48). Section 107(c)(4) provides that, so long as the manufacturer does not alter the drug's labeling, the addition of effectiveness to the defintion of "new drug" in Section 201(p) of the Act shall not apply to any drug which, on October 9, 1962: (A) was commercially used or sold in the United States; (B) was not a new drug as defined by the 1938 Act; *and* (C) was not covered by an effective application under Section 505 of that Act (J.A. 482). Petitioner contends that because a drug that was no longer a "new drug" had no further need of an effective application, it follows that such a drug's application was no longer "effective" within the meaning of Clause (C).

1. The first difficulty with petitioner's interpretation is, as the court of appeals stated (J.A. 176–177, citing J.A. 469–470), that it would render Clause (C)

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such a product could not meet Clause (B)'s requirement that it be generally recognized as safe on October 9, 1962. There is nothing bizarre or inconsistent in the conclusion that any drug that had ever required an effective NDA to be marketed prior to 1962 was excluded from the exemption of Section 107(c)(4)—by Clause (B) in the case of drugs with suspended NDAs and by Clause (C) in the case of those with effective ones.

entirely superfluous, since the simple fact that Clause (B) is satisfied would suffice to meet the requirement of Clause (C). Plainly, however, Clause (C) is a requirement additional to that in Clause (B), since Congress employed the conjunctive "and" in listing the requirements that had to be satisfied for the exemption. Thus, only the interpretation adopted by the court of appeals—that all applications that became effective between 1938 and 1962 were "effective" for purposes of Clause (C), unless their effectiveness had been suspended by FDA—gives rational meaning to the provision.

2. Petitioner does not, in fact, propose any alternative construction of Clause (C) that would give it meaning. Instead, it seeks to defend its construction by claiming that the possible alternatives are equally defective, either because Clause (B) would be rendered surplusage or because the entire exemption provision would not be given significant meaning (Br. 43–44). Both of these suggestions are, however, plainly in error. Clause (B) is obviously necessary to insure that drugs illegally on the market because no one ever procured an effective NDA for them would not be granted exempt status. And the government's interpretation of Clause (C) does not "defeat the intention of Congress to exempt some drugs from the effectiveness provisions of the 1962 Amendments" (Br. 44). As we explain in our brief in the *USV* case (pp. 49–52), the provision was intended to and does exempt drugs that, as a generic class, were never subject to new drug regulation—a category consisting primarily

of over-the-counter drugs which, because of changed composition or labeling, were not "grandfathered" under the 1938 Act, but, because of universal recognition of the safety of their old, established ingredients at the time they came on the market, were never subject to new drug regulation.

3. Hynson also errs in suggesting that its new drug application could not "in logic nor law" have been effective once the drug it covered ceased to be a new drug (Br. 40). Certainly the 1938 Act provided no mechanism, other than the Commissioner's suspension authority under Section 505(e), by which an NDA, once it became effective, would cease to be effective thereafter. Indeed, the wording of the suspension provision itself clearly establishes that an application would not cease to be effective under the Act when the drug ceased to be "new." The very contingency Section 505(e) contemplates is that evolving scientific knowledge may cast doubt upon the safety of a drug previously considered safe,[20] and the provision is designed to give FDA power to deal administratively with such a contingency. If the NDA ceased to be effective because the drug it covered had (temporarily) ceased to be new, how could its "effectiveness" be suspended when doubt was cast on its safety? Only by treating the NDA as having continuing effectiveness could administrative control through Section 505's regulatory procedures be retained. The statute thus clearly contemplated that the NDA would remain effective in this sense even if

[20] See our brief in *USV* at p. 48, n. 31.

inactive, and it is petitioner's effort to shed this status as a means of escaping efficacy regulation for its product that is not supportable "in logic nor law."

4. Hynson also suggests that the legislative history of the 1962 Amendments supports its position that Congress meant to exempt drugs that had become generally recognized as safe from efficacy regulation (Br. 45–48). However, Hynson never reconciles this suggestion with the clear congressional explanation in the Senate, House, and Conference reports that the exemption afforded by Section 107(c)(4) is for drugs that had *never* been subject to new drug regulation. See S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess., p. 8; H. Rep. No. 2464, 87th Cong., 2d Sess., p. 12; H. Rep. No. 2526, 87th Cong., 2d Sess., pp. 22–23; see also 108 Cong. Rec. 17366 (remarks of Senator Eastland). Lutrexin obviously fails to satisfy that congressional standard.

Moreover, to the extent inferences are to be drawn from the less explicitly applicable facets of the history of the 1962 Amendments, they show that Congress considered but ultimately refused to enact the wholesale exemption for which Hynson contends.

As originally reported by the Senate Judiciary Committee on July 19, 1962, the Amendments left the 1938 Act's definition of "new drug" in Section 201(p) unchanged. The new drug effectiveness provisions appeared solely in Section 505, to which was added the

requirement that, to obtain or retain an NDA, the manufacturer show substantial evidence of effectiveness. S. Rep. No. 1744, *supra,* Part 1, pp. 24–27. The effect of the bill in this version would have been that the manufacturer of a drug generally recognized as safe (*i.e.,* not a new drug) need not show that the drug is also effective. As the Senate report made clear, the bill was designed to protect such drugs in their current claims: "The Committee decided that it was unnecessary to add the requirement of 'effectiveness' to the definition of a new drug in section 201(p) * * *. If such a change were made in the definition of new drug, many 'old' established drugs might have to go through burdensome new drug clearance procedures even though their safety is unquestioned. That result is believed unsound." *Id.* at 17. Had this version of the bill become law, Lutrexin would indeed have been "grandfathered." However, it never became law.

Instead, President Kennedy, anxious to strengthen the bill, sent the Chairman of the Senate Judiciary Committee seven proposed amendments on August 4, 1962. 108 Cong. Rec. 15695–15698. The fourth proposed amendment called for the inclusion of "effectiveness" in Section 201(p)'s definition of "new drug" to "assure that all new drugs will have to be proved effective as well as safe for the uses for which they are offered * * *." *Id.* at 15696. The President also proposed a transition provision which would require "a commercially established drug to go through

the 'new drug' process" "if there is substantial doubt as to its efficacy." *Id.* at 15696.[21]

On August 21, 1962, the Senate Judiciary Committee reported a much strengthened version of the bill, with changes designed further to "insure the reliability of drugs." S. Rep. No. 1744, *supra,* Part 2, p. 1. In accordance with the President's suggestion, Section 201(p) now defined "new drug" to include effectiveness. *Id.* at 5. Sections 201(p) and 505 were thus made congruent in their use of a standard of effectiveness. Also in keeping with the President's suggestion, the Committee reported transitional provisions relating to drugs already on the market. These provisions, virtually identical to Section 107(c) as enacted, gave existing drugs which were generally recognized as safe but not generally recognized as effective a two-year grace period during which their NDAs were protected against withdrawal of approval for lack of substantial evidence of effectiveness. *Id.* at 7–8. The only type of drug which was exempted from the new requirements of effectiveness in Sec-

[21] The "substantial doubt" language gave way in the ultimate version of the legislation to the present language of "lack of substantial evidence." Thus, there was a modification in the standard by which the effectiveness of a drug was to be measured. But, contrary to Hynson's argument (Br. 45), this change in no way relieved pre-existing drugs of the need to prove effectiveness; it merely altered their burden or proof.

tions 201(p) and 505 was "* * * a new drug on the market which was never subject to the new drug procedure before * * *." *Id.* at 8.[22] The Senate then passed the bill with the effectiveness and transitional provisions as reported, and these were the provisions ultimately enacted.

This history thus establishes that Congress abandoned its original inclination to exempt "safe" pre-1962 drugs from the new drug effectiveness requirements, changing instead to a scheme under which all such drugs, unless grandfathered under the 1938 Act or coming within the narrowly defined exemption provided in Section 107(c)(4), were to be subject to efficacy regulation after the two-year grace period (presumably designed to afford manufacturers an opportunity to substantiate their products' claims by scientifically reliable investigations of the kind newly required in amended Section 505(d)).

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[22] Petitioner contends (Br. 46) that because Part 2 of the Senate report made clear that a new or changed claim for an existing drug would require submission to the Commissioner of substantial evidence of effectiveness, the Senate did not intend to subject already existing claims to the effectiveness requirements. This is incorrect. The committee, in the same paragraph which petitioner cites, referred readers interested in the effect of the amendment on existing drugs to the discussion of the transitional provisions. S. Rep. No. 1744, *supra*, Part 2, p. 5. And, as we have shown above, those transitional provisions gave no permanent exemption to existing drugs which had been subject to the new drug procedures under the 1938 Act, whatever their claims.

B. SECTION 107(C)(2) DOES NOT EXEMPT HYNSON FROM ADMINISTRATIVE WITHDRAWAL OF APPROVAL OF LUTREXIN'S NDA ON EFFECTIVENESS GROUNDS

Hynson also contends (Br. 38–41) that its application was not "effective" within the meaning of Section 107(c)(2), so that it was not "deemed * * * approved" by that provision and was accordingly not subject to withdrawal of approval under Section 107(c)(3). There is no basis for supposing that the word "effective" was employed in any different sense in Section 107(c)(2) than it was in Section 107(c)(4)—and Hynson makes no such suggestion. Accordingly, much of the foregoing argument is equally applicable to this contention.

Section 107(c)(2) was included in the transitional provisions for the simple reason that the 1962 Amendments altered the prior regulatory procedures, under which applications became automatically effective (unless the Commissioner refused to permit them to become effective) after the passage of a prescribed period of time. Amended Section 505 requires affirmative approval of applications. By providing that effective applications would be "deemed * * * approved" (J.A. 481), Congress eliminated the necessity that every application then in effect be reviewed and approved; it also protected the marketing authority of manufacturers that had effective applications, at least until such time

as the approval conferred by Section 107(c)(2) might be withdrawn under the provisions of Section 107(c)(3). Section 107(c)(2) is thus nothing more than a housekeeping measure to smooth the transition from the old regulatory standards to the new ones. There is no evidence that it was intended to go further and confer any form of substantive immunity from regulation, as Hynson suggests.

In any event, unless Hynson's interpretation of the exemption provision in Section 107(c)(4) is accepted (in which case the interpretation of Section 107(c)(2) is of no consequence), it is difficult to see what Hynson can gain by its interpretation of Section 107(c)(2). If Hynson's NDA was not "deemed * * * approved," that simply puts it in the same posture it is now in after withdrawal of approval under Section 505(e)—that of marketing an unapproved drug. All that Hynson could succeed in establishing, therefore, is that its marketing of Lutrexin has been illegal since the enactment of the 1962 Amendments, because it would no longer be able to claim approved status under Sections 107(c)(2) and 107(c)(3), which status persists until administrative withdrawal of approval.

CONCLUSION

For the foregoing reasons and the reasons stated in our brief in No. 72-394, the judgment of the court of appeals should be reversed and the order of the Commissioner of Food and Drugs withdrawing approval

of the new drug application for Lutrexin should be affirmed.

Respectfully submitted.

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APPENDIX A

Congressional Understanding of The Scientific Principles Underlying Adaquate and Well-Controlled Investigatons To Prove Drug Effectivness.

The scientific principles underlying adequate and well-controlled clinical investigations were described in detail to Congress during its consideration of the Drug Amendments of 1962 and formed the basis for the statutory requirements for proof of drug effectiveness. This Appendix sets forth excerpts from the large body of testimony of distinguished scientists, as well as representatives of the drug industry itself, urging upon Congress the importance of establishing scientifically valid criteria for evaluating drug effectiveness. Congress adopted these expert recommendations by incorporating the definition of "substantial evidence" of drug effectiveness in Section 505(d) of the Act.

1. On April 20, 1960, Dr. Austin Smith, President of the Pharmaceutical Manufacturers Association, appeared before the Senate Subcommittee on Antitrust and Monopoly. In the course of his testimony, an article co-authored by him was placed in the record: Smith et al., *Laboratory and Clinical Appraisals of New Drugs,* from the Journal of the American Medical Association, December 9, 1944.[1] While the authors acknowledged that clinical investigation of new drugs presents difficult

[1] Hearings on Administered Prices before the Subcommittee on Antitrust and Monopoly of the Senate Judiciary Committee, 86th Cong., 2d Sess., 10986–10991 (1960).

problems, they suggested that certain factors be considered:

(*a*) *The Selection of Individuals to be Observed.*—Cooperation from subject; absence of complicating factors; age; sex; emotional and psychic factors.

(*b*) *Diagnosis.*—Objective proof of diagnosis if possible, such as isolation and identification of infecting organism; x-ray evidence or other informative laboratory data; accurate description of lesion; differential diagnosis.

(*c*) *Control Observations.*—Preliminary control observations on the individuals; concurrent observations of untreated controls; alternation of treatment; alternation of treated and control subjects; posttreatment, control observations.

(*d*) *Observation During Treatment.*—Repeated physical and laboratory examinations; hematology; urinalysis; blood chemistry; x-ray; functional tests; precise objective measurements of improvements alleged to be produced by drug; determination of concentration of drug in blood, urine and other body fluids and the correlation of levels so observed with the dosage and the effect.

(*e*) *Number of Subjects.*—Sufficient number of treated individuals to minimize chance or other uncontrollable factors from influencing results; sufficient number of untreated control subjects. The results should be subjected to statistical analysis in order to determine their reliability.

(*f*) *Carefully Planned Administration of Drug.*—Controlled variation in dosage, frequency, method and duration of administration; effect of other drugs, and so on.

(*g*) *Criteria of Benefit.*—Establishment of criteria whereby the effects of the drug may be evaluated; objective tests; subjective observations; comparison with control treatments; comparison with natural course of disease.

(*h*) *Separation of Subjective and Objective Observations.*—Use of "blind tests" (neither investigator nor subject knows which of several samples being administered is control or test product) or other methods to eliminate conscious or unconscious bias on part of observer and subject; careful separation of symptomatic reactions from objective findings; psychologic appraisal of subject.

(*i*) *Duration of Observation.*—Treatment to continue until any intrinsically undesirable or harmful manifestations have had time to develop as well as until sufficient time has elapsed to demonstrate beneficial effects; comparison of rapidity of cure or improvement with that of other methods of treatment.

(*j*) *More Than One Clinical Investigation.*—Several different investigators working independently; conclusions to be made independent of one another's results.

2. During its 1961 hearings, the Subcommittee heard extensive testimony on the scientific basis for proving drug efficacy.[2]

Dr. Charles D. May, Professor of Pediatrics, New York University Medical School, testified to the "fallacy" of assuming that "a collection of impressions" will furnish the truth, pointing out that "this approach did not prevent doctors from having unbounded faith in the curative powers of leeches for hundreds of years before scientific evaluation became the preferred means of judging efficacy of therapy." He testified that the "magnitude of sales of a drug after vigorous promotion is no recommendation for its usefulness or efficacy" and recommended that "the

[2] Hearings on Drug Industry Antitrust Act before the Senate Subcommittee on Antitrust and Monopoly of the Senate Judiciary Committee, 87th Cong., 1st Sess., pursuant to S. Res. 52 on S. 1552, Pt. 1 (1961).

present concept of controlled methods of evaluation of drugs" be employed to determine efficacy.[3] He reasoned that "in modern times the methods required for scientific evaluation of a drug require design of experiments, controlled experiments, beyond the facilities of each and every individual physician,"[4] that "an orderly approach of experimental evaluation would be a vast improvement over wanton individual experience,"[5] and that efficacy is "unlikely" to be determined unless a drug is tested "by a systematic, scientific evaluation according to the best modern procedures."[6]

Dr. Louis Goodman, Professor of Pharmacology, University of Utah College of Medicine, and coauthor of "The Pharmacological Basis of Therapeutics," said that those who had seen "the mass of laboratory and clinical information submitted to the FDA, even by the very best drug houses, in support of new drug applications are repeatedly dismayed by the welter of anecdotal case reports and uncontrolled clinical studies;"[7] that the "average practicing physician—and I have helped to train hundreds of them—just does not have the time, the facilities, the skill, nor the training to be an expert in the determination of drug efficacy."[8] Dr. Goodman insisted upon "basic, original, clinical evidence that [a] drug is a useful drug and that the claims made by the manufacturer are valid." He noted that 35 out of 100 people react to placebos, and "that is why experts talk in detail about controlled clinical

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[3] *Id.*, pp. 195–196.
[4] *Id.*, p. 204.
[5] *Id.*, p. 205.
[6] *Id.*, p. 207.
[7] *Id.*, p. 215.
[8] *Id.*, p. 217.

experiments; that is why the individual practicing doctor cannot be the judge." [9]

Dr. Louis Lasagna, head of the Division of Clinical Pharmacology at Johns Hopkins, testified that in "some areas of disease, it is easier to devise adequate tests than in others. Yet it remains a basic principle that in the absence of measurable evidence that two drugs differ, one must assume that the two drugs are alike. * * *

"Because I have often testified to the importance of double-blind controlled trials in clinical research, some may consider my statements to constitute a demand for uch trials on all new drugs. Not at all. There are certain areas of disease—insomnia, anxiety, depression, and pain, for example—where the absence of such controlled trials leads to, in my opinion, chaos. In some other areas—acute leukemia, for example—an answer might be easily obtainable in a small number of patients without the use of double-blind controls. The emphasis should be on scientifically acceptable evidence." [10]

On this point he asked: "What of the allegations that only by extensive clinical experience can the true efficacy of a drug be established? The history of medicine is, unhappily, replete with examples of useless drugs employed for years, decades, or centuries, by countless physicians before a few properly conducted experiments proved the drugs to be without value." [11]

Dr. Allan M. Butler, Professor of Pediatrics, Harvard Medical School, commented that "It is very hard * * * to have a private, practicing physician in his private practice properly appraise the efficacy and toxicity of a drug.

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[9] *Id.*, p. 243.

[10] *Id.*, pp. 282–283.

[11] *Id.*, p. 283.

"It must be done by physicians who have the facilities to set up controlled clinical testing. * * * "[12]

Dr. Harry F. Dowling, Professor and Head of the Department of Medicine, University of Illinois, testified on minimizing patient and investigator bias, on placebo effect, and on double-blinding. He related the following example:

> It is a well-known fact that if the physician gives a patient a drug and tells the patient or otherwise implies to him that this drug is going to make him better, an appreciable percentage of the patients will indeed feel better and will insist that the drug has caused the improvement. This is the placebo effect.
>
> Thus, if a new tranquilizer drug were to be tested, a certain number of patients should be given an inert substance which looked exactly like the tranquilizer, and neither they nor the doctors evaluating the drug should know who received the dummy and who received the real drug. Only by this method could the efficacy of such a drug be tested properly.[13]

He emphasized that comparative analysis between patient groups is necessary "in order to determine that the differences in the case fatality rates were due to the [drug] and not due to chance alone"; that the "proposed bill would make sure that the proper tests had been done * * *."[14] He concluded:

> Anything that would improve the practice of medicine would benefit the patient. If more adequate tests are done to determine the efficacy of a drug, the patient benefits; if claims for a drug coincide with proved accomplishment, the patient benefits, and if the doctor knows what drug he is prescribing, what it will

[12] *Id.*, p. 355.
[13] *Id.*, p. 411.
[14] *Id.*, p. 412.

do and what the possible toxic reactions are, the patient obviously benefits.[15]

Dr. Maxwell Finland, Associate Professor, Harvard Medical School, observed that, with "respect to the use and evaluation of drugs, the practicing physicians must, as in other areas, rely on those with more experience and those who have special knowledge, training and experience and who have the facilities and opportunities to make the necessary observations and comparisons that are required to make a reliable judgment. If he is honest, the individual physician will admit that he can only gather impressions concerning the effect of the remedy he uses in an individual patient, but he cannot even in that case determine the likelihood that the response was a matter of chance or was due to any of the different methods of treatment that he employed, nor can he say what might have been the result were some other drug used. Only when adequate numbers of properly studied cases are gathered and the responses analyzed and compared with similar data from other well documented experiences can one gain some approximation of the true effectiveness of any remedy." [16]

Dr. Finland illustrated the need for adequate and well-controlled studies by giving the example of 100 reported staphylococcal pneumonia patients treated with drug X, none of whom died, although the best alternative drug available still resulted in 50% mortality. Drug X was hailed as a wonderful new treatment. The physician had done lab tests and determined the presence of staphylococcus before administering treatment, but no X-rays were taken to confirm the diag-

[15] *Id.*, p. 424.
[16] *Id.*, p. 430.

nosis. Upon closer scrutiny, no patient was found actually to have had staphylococcal pneumonia:[17]

> Now, this is the type of evidence that is presented to the FDA and which the FDA is told: "Now, look, you are taking thousands and thousands of cases and you are pitting these against a few studies." They do not say "careful" or "controlled" studies. They say "a few cases" by some experts, so-called, only people who think that they are experts. This is the sort of material they are presenting to you.
>
> This is the sort of thing that I say is dangerous because another doctor who knows how to make a diagnosis of staphylococcal pneumonia will use that drug to the peril of this patient.

Eugene N. Beesley, President of Eli Lilly & Co. and Chairman of the Pharmaceutical Manufacturers Association, testified that "we support the principle that, before introducing a new drug, the manufacturer should be required to submit to the Food and Drug Administration substantial evidence not only that the drug is safe but also that it produces the results claimed. * * * The test of effectiveness is to be whether the drug will produce the specific effects asserted by the manufacturer."[18] He stated that "[t]he key words are 'well-conducted clinical trials by competent clinicians.' "[19]

3. After enactment of the 1962 Amendments, Congress continued to reflect its interest in the requirement of adequate scientific evidence to show drug effectiveness. In S. Rep. No. 1153, 89th Cong., 2d Sess. (1966), the Committee investigating Interagency Drug Coordination made the following observations (pp. 197-200; footnotes other than 86a omitted):

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[17] *Id.*, pp. 450–451.

[18] *Id.*, Pt. 4, pp. 1996–1997. See also pp. 1998–1999.

[19] *Id.*, p. 2007. See also p. 2012.

5. *Authorities' Insistence on Controlled Clinical Trials.*—Scientific authorities believe that, with certain exceptions, efficacy of a drug should be proven on the basis of a controlled clinical experiment; i.e., an experiment based upon comparison of results—those obtained by the drug as contrasted with those obtained, in a comparable group of patients, by either a blank pill (with inert ingredients; i.e., a placebo) and/or standard therapy.[86a]

University authorities on testing hold to the view that a drug may be regarded as truly *efficacious* only if its use yields better results (in a significant statistical sense) than those obtained from a placebo in such an experiment.

* * * * *

A careful scientific experiment requires, they note, other elements; e.g., (*a*) careful biostatistical preparation and analysis; (*b*) *randomized selection* of similar patients into groups which are to receive the drug being tested and the placebo; (*c*) careful withholding of knowledge from the patient as to whether he is being given an active drug or placebo; (*d*) careful efforts to withhold from the investigator the identity of the drug (if the experiment is to be, by definition, of a double-blind character).

Danger of Bias.—These elaborate procedures have been devised as a means of overcoming a wide variety of factors which, over the years, had led to erroneous belief in therapy which later proved to be worthless. Most notable among these factors has been what is known as the placebo effect. This refers to the potentially powerful

[86a] Comparison is not always either necessary or possible. For example, a physician treating a patient with a disease whose course is certain to be fatal and for which no alternative therapy is available, might decide that it would be contrary to medical ethics to give a mere placebo to a "control" group of such doomed patients. Most clinical conditions do not, however, involve circumstances ruling out a control.

effect of belief in a drug. It derives from suggestibility of a patient—his expectation that a drug will "cure" him. * * *

A second factor which the controlled experiment is designed to eliminate is the bias of the investigator, intentional or unintentional.

Most such bias is unwilling on the investigator's part. It derives from his own desire to discover a genuinely efficacious drug. His enthusiasm tends to "color" his observations.

* * * * *

6. *Dispute Over Science by "Majority Vote."*—Many university authorities contend that credence cannot be placed in what are termed "clinical impressions" no matter how many hundreds or even thousands of physicians may offer them as "proof" of a drug's value.

* * * * *

A dozen years ago, a distinguished British scientist, Sir Austin Bradford Hill, stated: * * *

> Two or three uncontrolled observations may give, merely through the customary play of chance, a favorable picture in the hands of one doctor, an unfavorable picture in the hands of a second. And so the medical journals, euphemistically called the "literature," are cluttered up with conflicting claims—each in itself perfectly true of what the doctor saw, and each insufficient to bear the weight of the generalization placed upon it.

Professor Louis Lasagna has criticized supporters of such "clinical experience" * * *:

> There is a common belief that the addition of many bits of disorganized data will somehow yield a clear picture, that the multiplication of zeros (or near zeros) will somehow produce an important finite good. Unfortunately, the his-

tory of therapeutics gives scant support to such philosophy. In medicine, theories and therapeutic practices, including those espoused by the majority come and go. One generation bleeds the ill, another scoffs at bloodletting. One generation insists on prolonged bedrest, another preaches the dangers of immobilization and the benefits of early ambulation for everything from surgery to cardiac infarct. * * * There thus can be no sense of confidence automatically generated by "traditional" practice; in therapeutics, as in many other areas of human endeavor, there is no magical safety in numbers.

It is a sad fact that the individual physician cannot really gauge the true worth of many remedies. There are, to be sure, clinical situations where the course of the illness is so stereotyped and predictable that a drug-induced change is readily appreciated. In such cases, the doctor can be his own judge and jury. But in many situations, the patient's disease has spontaneous and erratic ups-and-downs or is self-cured at unpredictable rates of improvement or responds dramatically to suggestion and the impact of the doctor-figure. In these instances, it is difficult enough to assess remedies with a strict experimental design; it is sheer bravado to draw conclusions without such a plan.

On another occasion, Dr. Lasagna stated * * *:

* * * it is almost certain that the "experts" do not subscribe to the AMA's democratic notion that "only the medical profession, after widespread usage, can determine the true effectiveness of a drug." *Scientific truth is not arrived at by majority vote. There is too much evidence that the medical profession, like*

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the rest of us, can be misled by "practical experience" to encourage the testing of truth by referendum. * *

The amassing of unsubstantiated views of practitioners is regarded as inconclusive and generally unworthy of scientific debate. Critics liken such unworthy "evidence" as equivalent to "testimonials," such as medicine, itself, long fought in patent medicine advertisement.

Debate Over Antibiotic Combinations.—University experts criticize, for example, what they regarded as unjustified medical protests which poured in on FDA because an expert advisory committee objected to antibiotic combinations for treatment of upper respiratory infections. The experts assert that no matter what the number of protests, 400, 1,000, or more, such subjective views by M.D.'s cannot possibly refute the advisory committee's judgment that there is no scientific proof of these combinations' efficacy. University experts feel that FDA should not be so easily influenced by masses of protests, considering that the protests may not contain a shred of scientifically controlled evidence.

APPENDIX B

The Scientific Principles Underlying Adequate and Well-Controlled Clinical Investigations To Prove Drug Effectiveness

The Federal Food, Drug, and Cosmetic Act requires that all drugs be effective for their labeled indications. A drug must either be generally recognized as effective or approved for effectiveness by FDA.[1] To explain the basis upon which FDA determines effectiveness, the Commissioner of Food and Drugs published regulations outlining principles developed over a period of many years by investigators actively engaged in the evaluation of the therapeutic efficacy of drugs.[2] This appendix summarizes the scientific basis for these principles.

Although in the earlier part of this century there were occasional calls for more scientifically acceptable methods in the clinical evaluation of drugs,[3] development of the principles of the controlled clinical trial and their actual application did not gain impetus until the time of World War II.[4] Great strides

[1] 21 U.S.C. 321(p), 355 (d) and (e).

[2] 21 C.F.R. 130.12(a)(5).

[3] Irons, *The Clinical Evaluation of Drugs*, 93 J. Am. Med. Assn. 1523–1524 (November 16, 1929); Leake, *The Pharmacologic Evaluation of New Drugs*, 93 J. Am. Med. Assn. 1632–1634 (November 23, 1929).

[4] Atkins, *Conduct of a Controlled Clinical Trial*, Brit. Med. J. no. 5510, at 377–379 (August 13, 1966); Van Winkle et al., *Laboratory and Clinical Appraisal of New Drugs*, 126 J. Am. Med. Assn. 958–961 (December 9, 1944); Gold, "Experience in Human Pharmacology," in *Quantitative Methods in Human*

have been made in therapy in the past without the benefit of this experimental device, simply on the basis of the uncontrolled observations of astute clinicians. Modern controlled clinical trials were not needed to establish that such important drugs as digitalis, ether, penicillin, quinine, and the sulfonamides had therapeutic effectiveness. Controlled trials were, however, needed to define the exact therapeutic roles of these drugs. Further, thousands of drugs which, on the basis of "clinical experience," were once accorded an "indispensable place" in therapy, are now known to be useless as the result of controlled trials. Many of these subsequently discarded agents and therapies (gold therapy in tuberculosis, violent purging, bleeding, total colectomies for "autointoxication") lingered on for great periods of time in the practice of medicine, and were not only inefficacious, but seriously injurious or occasionally lethal for some patients.[5]

The function of the formal controlled clinical trial is to separate the relative handful of discoveries which prove to be true advances in therapy from a legion of false leads and unverifiable clinical impressions, and to delineate in a scientific way the extent of and the limitations which attend the effectiveness of drugs. The importance of properly conducted, controlled tests as the only reliable method of evaluating drug effectiveness in most instances is a theme constantly expressed in modern writing on pharmacology:

> Let me try to recapitulate briefly. Why are controlled trials important? Because few dis-

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Pharmacology and Therapeutics (1959); Gaddum, *Clinical Pharmacology*, 47 Proc. Royal Soc. Med. 195–204 (1954); Barber, *Drugs and Society* 19 (1967).

[5] Atkins, *supra;* Pickering. *The Place of the Experimental Method in Medicine*, 42 Proc. Royal Soc. Med. 229–234 (1949).

eases run a course which is precisely predictable; because patients, doctors, and details of medical care differ greatly from place to place, and from one time to another; and because most patients and most physicians are biased towards expecting therapeutic benefit. A properly designed trial is, therefore, an attempt to safeguard the investigator from unwarranted conclusions. The double-blind aspect of experimental design is only one facet of the problem. The principles of concurrent comparison of treatments, of unbiased allocation of patients to treatment groups, and of statistical analysis of data are equally important. Will adherence to these principles insure a successful experiment? Of course not. One still has to ask an appropriate and answerable question. But the chances of reaching a correct answer are considerably greater when the above principles are adhered to.[6]

* * * * *

In order to decide whether patients treated in one way are benefited more than those treated in another, there is no possibility of avoiding the use of numbers. The mere statement by a clinician that patients do better with this or that treatment is due to his having formed an opinion that more patients are helped by the treatment he advocates than by other treatments. The opinion is based on numbers, but having omitted to record exactly how many patients have been treated by different methods and having omitted to ensure that the only variable factor affecting the patient was the treatment in question, only a "clinical impression", instead of a scientific fact, can be stated. This is a pity, for progress is delayed when convinced opinions are offered in place of

[6] Lasagna, *Controlled Trials: Nuisance or Necessity*, 1 Meth. Inform. Med. 79, 81 (1962).

convincing facts. The former, though not necessarily wrong, are unreliable, despite the great assurance with which they are often advanced.[7]

* * * * *

It is the judgment of competent authorities that the relative effectiveness of specific therapeutic measures can be reliably established only in well-controlled comparative clinical investigations. These embody the following essential procedural steps in the design of the study: descriptions of all the patients in the total sample; random allocation of them so as to provide adequate, suitable and comparable control as well as therapeutic groups; standardized criteria of therapeutic effectiveness.[8]

* * * * *

The history of medicine abounds with remedies that were long and widely used before falling into disrepute and vanishing. A designed test might have greatly hastened their fall from favor and have thereby encouraged the search for something better.

It is these situations that the controlled clinical trial is designed to meet.[9]

* * * * *

Well controlled clinical evaluations reflecting the above ideas are not the invariable rule in practice today. Indeed, some resistance to the very concept often arises. The traditional authoritative attitudes held by most physicians make it difficult for them to believe that they cannot put complete trust in their individual

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[7] Laurence, *Clinical Pharmacology* 11 (2d. ed. 1963).

[8] Committee on Public Health, New York Academy of Medicine, *The Importance of Clinical Testing in Determining the Efficacy and Safety of Drugs*, 38 Bull. N.Y. Acad. Med. 415, 426 (1962).

[9] Hill, "Aims and Ethics," in Council for International Organizations of Medical Sciences, *Controlled Clinical Trials—A Symposium* 3 (1960).

judgments but must defer to the conclusions of some nearly unknown investigator. However, the individual physician combining the responsibilities of evaluation with those of patient care is easily misled by "mere experience," and an acceptable evaluation can be done only by executing a carefully prepared experimental design.[10]

* * * * *

What constitutes an adequately controlled clinical trial necessarily varies, depending upon the drug effect being evaluated. The more important general requirements for all trials are an appropriate and adequately sensitive method of evaluation, an adequate number of subjects, lack of bias, concurrent comparison of the new drug with a reference drug over a range of doses, and appropriate statistical validation. Depending upon the drug effect being evaluated, sore clinical trials must be conducted under so-called blind conditions.[11]

* * * * *

We have what we call our clinical experience. The difficulty about clinical experience as I have known it in my own case and vicariously in the case of my colleagues is that, in a general way, it is unplanned and haphazard. We are victims of the freaks of chance. We may have a little run of experience which convinces us that a certain treatment is the most useful. We are also victims of the attractive propaganda leaflets that arrived from the drug companies the week before and of the persuasive eloquence of our colleagues. And so, working in this way, we often, in good faith, carry out a treatment for a considerable time and at the end of it we do not

[10] Meyers et al., *Review of Medical Pharmacology* 15 (1968).

[11] Fingl & Woodbury, "General Principles," in Goodman & Gilman, *The Pharmacological Basis of Therapeutics* 1, 30 (1965).

know whether our treatment has done our patients any good or not * * *

To my mind, then, the clinical trial is the best way of getting to know what are the probabilities that a given form of treatment will affect one's patient for better or for worse.[12]

* * * * *

The field of medical observation, it is necessary to remember, is often narrow in the sense that no one doctor will treat many cases in a short space of time; it is wide in the sense that a great many doctors may each treat a few cases. Thus, with a somewhat ready assumption of cause and effect and, equally, a neglect of the laws of chance, the literature becomes filled with conflicting cries and claims, assertions and counterassertions. It is thus, for want of an adequately controlled test, that various forms of treatment have, in the past, become unjustifiably, even sometimes harmfully, established in everyday medical practice.[13]

In the discussion that follows, we outline the ten scientific principles that experts in pharmacology have enunciated as the requirements for and characteristics of an adequate and well-controlled clinical investigation. These principles form the foundation of and are embodied in the Commissioner's regulations interpreting the drug effectiveness evaluation standards. See also, Doll, "Clinical Trials," in Zaimis & Elis, *Evaluation of Drugs in Man* 159 (1965); Sheps, *Problems in Clinical Evalation of Drug Therapy*, 5 Perspectives in Biol. Med. 308, 361 (1962).

1. *There must be a plan or protocol for the study.*

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[12] Pickering, in Council for International Organizations of Medical Sciences, *supra*, at 164.

[13] Hill, *Statistical Methods in Clinical and Preventive Medicine* 4 (1962).

It is impossible to make any meaningful evaluation of the evidence from a clinical trial unless the reviewer has a detailed plan or protocol of the study at his disposal. This protocol must explain the objectives of the study, the complete methodologic details of how the study was done, and how the data were collected and analyzed.

> As the controlled clinical trial stands or falls on its plan, the report must describe this in detail. It is important to give the diagnostic criteria employed, so that it is evident that the patients selected were homogeneous in respect of their illness, and so that it is obvious in what clinical conditions the results of the trial might later be applied. The recruitment of patients, whether for example from all admissions to the wards or out-patients which satisfy the diagnostic criteria, or from some special source, and the method of allocation to Treated and Control groups, require special attention on the report as this is the crucial stage in a trial. The therapeutic regime to be given to both groups must be stated, in particular whether the dose is to be fixed or left to the physician's discretion, together with the reasons for this decision * * * The plan also includes the choice of clinical and laboratory tests used to measure the patient's progress, their timing and the scales by which they are to be interpreted, and the arrangements made to ensure equality of observation, both objective and subjective, on the Treated and Control groups.[14]
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> * * * * *
>
> . . . a written plan should be made which states the objects of the trial, the principles underlying the plan, the criteria for admitting

[14] Knowelden, "The Analysis and Presentation of Results," in Council for International Organizations of Medical Sciences, *Controlled Clinical Trials--A Symposium* 155 (1960).

patients, exact details of how to proceed and instructions about what information is to be collected and how it is to be recorded. Specimen documents for the recording of the data should be attached to the plan. . . .[15]

(2) ***The plan or protocol must include a clear statement of the objective of the study.***

The importance of a clear formulation of the basic question or questions to be answered by the clinical trial is emphasized by many authorities.

> The first step in the controlled trial is to decide precisely what it sets out to prove. It is essential that initially its aims should be laid down in every detail.[16]
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> * * * * *
>
> The precise goals and objectives of any clinical research project must be clearly specified at the very outset * * * Only by formulating the correct questions can the monitor and the investigator achieve the answers they seek. And it is these answers that are the primary objects of the clinical trial.[17]
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> * * * * *
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> The choice of the primary objects of the trial is of profound importance. They should be chosen after considering what is already known of the course of the disease and the effects of established treatments.[18]
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> * * * * *

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[15] Truelove, "Therapeutic Trials," in Witts, *Medical Surveys and Clinical Trials* 148, 150 (2d ed. 1964). See also Cox, *Planning Clinical Experiments* 55–72 (1968); Hill, *Statistical Methods in Clinical and Preventive Medicine* 25 (1962).

[16] Hill, *Principles of Medical Statistics* 251 (8th ed. 1966).

[17] Taber, *Proving New Drugs* 78 (1969).

[18] Truelove, *supra*, at 149.

The first step in the design of a therapeutic trial is the formulation of the questions that it is hoped to answer. It is wise to limit the number of questions and to make these few absolutely precise. This has the disadvantage that the answers are limited to specific questions and are unsuitable for generalizations. On the other hand, if the questions are made too complex, the investigator will be unable to draw any firm conclusions at the end of the trial. He will be faced with a number of inconclusive answers, each based upon too few observations. In short, the exact aim of the trial should be thought out in detail before it is begun. This will involve such points as the accurate description of the patients to be included in the trial, the treatment(s) that they are to be given, and the measurements that are to be made to reveal the progression of their illness and the effects, if any, of the drug.[19]

(3) *The plan or protocol must include a method of selection of the subjects that provides for adequate confirmation of the disease state present, including criteria of diagnosis and appropriate confirmatory laboratory tests.*

Since the clinical trial is intended to predict on the basis of experience with a small sample of patients with a given disease, what the response of the generality of patients with that disease will be to a specific treatment, it is essential that the protocol define the disease with extreme care. Accurate diagnosis

[19] World Health Organization, *Principles for the Clinical Evaluation of Drugs*, Tech. Rep. Ser. No. 403, at 21 (1968). See also Laurence, *supra*, at 15; Lasagna & Meier, "Experimental Design and Statistical Problems," in Waife & Shapiro, *The Clinical Evaluation of New Drugs* 37, 38 (1959); Hill, *The Clinical Trial*, 190 Practitioner 85, 86 (January 1963); Cox, *Planning Clinical Experiments* 14, 57 (1968).

of the disease is also important. Since the diagnosi of most disease entities is not absolutely clear cu the particular diagnostic criteria used by the investi gator must be presented. In those diseases in whic laboratory tests may prove of material aid in accurat diagnosis, these tests should be done and their result reported.

> The first area to work upon will be the exac definition of the clinical problem to be tackled The patient and disease expected to be deal with must be identified accurately for the re sults to be meaningful to others. It is not enough to talk vaguely of hypertension or wound infection or rheumatoid arthritis, for there are multiple degrees and stages of disease. Without precision of original definitions there can be no precision transmitted in the conclu sions, no matter how carefully all the interme diate steps have been measured.
>
> The definition of the disease must be written down, and the necessary and sufficient criteria for a diagnosis accepted. Clinical diagnosis are not always possible in clear-cut terms, for con flicting evidence must be weighed, and absent features considered in relation to the grossness of those features present. Yet, if this experi ment is to be meaningful to others who did not examine these patients, then some definite de siderata must be met in all patients.[20]
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> * * * * *
>
> The problem of diagnosis and exclusions is broad and recurrent. Diagnosis is a difficult art, and the problem of correct diagnosis is worse, not better, when one is conducting a thera peutic trial. If the patient's response to therapy is used to judge the usefulness of that therapy in future patients who have the same disorder as the one incorrectly diagnosed in the first

[20] Cox, *supra*, at 16.

patient, a great deal of future mischief may result. One must therefore set up criteria for diagnosis and exclusions that will prevent admission of patients with diseases that are superficially similar to, but fundamentally different from, the disease under study.[21]

* * * * *

Regardless of the size of the aggregation, therapeutic comparison cannot be fruitful unless the two groups of patients to be studied are more or less homogeneous. The chief prerequisites for homogeneity are uniform etiology and pathogenesis in the two comparison groups.[22]

* * * * *

. . . the investigator will need to consider such questions as accuracy of diagnosis and severity of disease in patients to be admitted to the trial, whether the patients have a history of therapy that might medify the course of their illness and thus, possibly, confuse the issue of the trial, whether they should be limited to defined area (e.g., excluding the very young or old), whether they should be without other diseases than the one under investigation, and so on.

The criteria must not, of course, be made so rigid as to limit unduly the patients available for the trial, nor to make the answer to the trial so narrow as to be of little use in medical practice.[23]

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[21] Carr, *Practical Considerations in the Design of Clinical Trials*, 98 Canad. Med. Assn. J. 307, 311 (February 10, 1968).

[22] Martini, "Experimental Design in Clinical Medicine," in Ladimer & Newman, *Clinical Investigation in Medicine: Legal, Ethical and Moral Aspects* 398, 400 (1963).

[23] World Health Organizations, *supra*, at 21. See also Taber, *supra*, at 80. Truelove, *supra*, at 150, Fletcher, "Criteria for Diagnosis and Assessment in Clinical Trials," in Council for International Organizations of Medical Sciences. *Controlled Clinical Trials—A Symposium* 19, 20, 27 (1960).

The considerations relevant to the definition of the population of patients used in a study have been discussed,[24] and the problems of the taxonomy of disease and how these relate to clinical trials have been explored, in great depth.[25]

(4) *The plan or protocol must include a method of selection of subjects that provides for assignment of the patients to test groups without bias.*

The concept that patients should be allocated to treatment groups in such a way as to minimize the risk of bias is central to the controlled clinical trial. In the words of one researcher, "It is difficult to conceive of a rule more important for the clinical investigator than that of avoiding bias in the allocation of cases to different treatment groups." [26] In the framework of the clinical trial, "bias" is introduced into the experiment to the extent that known or unknown variables capable of influencing treatment outcome are unequally distributed between treatment groups. Bias is thus something more than the conscious or unconscious prejudices of the investigator, observer, or subjects.[27]

The distinctive feature of an experiment is that the investigator comparing the effects of two or more factors assigns them himself to the individuals who comprise the test population, and he can assign these factors in such a way as to reduce the risk of bias to a predetermined degree.[28] Reducing the risk of bias in-

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[24] Mainland, *Elementary Medical Statistics* 29–38 (2d ed. 1963).

[25] Feinstein, *Clinical Judgment* (1967).

[26] Lasagna, *The Controlled Clinical Trial: Theory and Practice*, 1 J. Chronic Dis. 353, 356 (1955).

[27] Houde et al., "Clinical Measurement of Pain," in deStevens, *Analgesics* 75, 80 (1965).

[28] Mainland, *Elementary Medical Statistics* 19 (2d ed. 1963).

volves more than the mere matching of attributes known to be capable of influencing results, for this would not ensure that hidden variables are equally distributed. Only deliberate randomization ensures the chance distribution of hidden variables. If randomization is properly performed, and if chance can be ruled out as the likely cause of observed treatment difference, then the cause of the difference can reasonably be attributed to the treatment. On the other hand, if proper randomization in the allocation of patients to treatment groups has not been performed, an observed difference in the response of the treatment groups, even though statistically "significant," may be due either to the treatments or to the bias. In such a circumstance, one cannot reasonably attribute the observed difference solely to treatment differences, and hence a conclusion of treatment efficacy is unwarranted.

There are a few circumstances in which the random allocation of patients to treatment groups is not absolutely necessary, but these almost always correspond to those situations in which a historical control would be considered a satisfactory standard of comparison for a test treatment. No expert in the fields of biostatistics or clinical pharmacology disputes the crucial importance of the method of assignment of patients to treatment groups in determining whether a particular clinical trial constitutes an adequate and well-controlled investigation.

> Method of allocating patients to different groups, or of assigning different treatment to different patients, are subject to both conscious and unconscious bias if they depend on a physician's choice. Some method of random allocation is essential to avoid this danger. Commonly, this is achieved by the use of tables of random numbers, where each digit or each combination

of a given number of digits has an equal probability of selection * * *

The purpose of randomization is twofold: (1) to render the subject groups as equivalent as possible in regard to all variables other than the treatment under study, and (2) to provide scientific justification for the application and interpretation of statistical tests of probability and significance.[29]

* * * * *

One noticeable feature of the modern controlled trial is the allocation of patients to treated or control group by some entirely random method. . . .

The object is to produce two (or more) groups of patients similar in respect of any known or unknown characteristics that may affect the prognosis of their illness but differing in their treatments.[30]

* * * * *

Randomized designs, in which the order of entry of patients into a study is determined by chance, are often more useful than systematic designs, with preset order of entrance into the trial, for systematic designs are liable to systematic errors; i.e., the selection system may have a built-in bias, unknown to the investigator.[31]

* * * * *

The best way of getting equivalent groups is by allocating patients to them by "random allocation". To allot patients alternately or otherwise systematically is not satisfactory as the physician almost inevitably knows into what treatment group a patient will go whilst engaged in deciding whether the patient should enter the trial, and he may be unconsciously

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[29] World Health Organization, *supra*, at 22.

[30] Hill, *The Clinical Trial*, 190 Practitioner 85, 88 (January 1963).

[31] Carr, *supra*, at 309.

influenced by this if he has strong feelings about either the patient or the value of the respective treatments. With random allocation the treatment group into which the patient goes is only discovered after it as been decided to enter him in the trial.[32]

* * * * *

The patients are assigned treatments randomly—from a table of random numbers, or by birth date (or month)—odd dates on treatment A, even dates treatment B, or by a roulette wheel. There is no valid reason for the investigator to know what the randomization scheme is. Patients are not assigned alternately. They are not assigned haphazardly.[33]

* * * * *

No high-powered analysis of data will compensate for data of poor quality or dubious validity. A prime assumption in the statistical analysis of the comparative performance of two drugs is that there has been no bias in the allocation of patients to one particular treatment group. It is impossible to interpret a "statistically significant difference" between drugs if the therapeutic challenge has been made more difficult for one treatment by purposeful shunting of even occasional patients into that group. In such a case, Drug A may look better than Drug B either because it is better than B, or because the patients getting Drug A were less ill than those getting B. Since there is no way to distinguish between these alternatives, such an experiment is usually worse than useless.

The "random" assignment of patients required for a valid comparison must not be interpreted in the lay sense of "haphazard."

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[32] Laurence, *supra*, at 15.

[33] Schneiderman, "Defensive Design of Clinical Trials," in Sternberg & Newcomer, *The Evaluation of Therapeutic Agents and Cosmetics* 66, 68, (1964).

> Schemes such as alternation of subjects or odd and even serial numbers are notoriously subject to bias in assignment of patients. That they are often a minor gain in convenience is poor payment for the loss of an objective measure of error. Although an investigator may convince himself that there is no conceivable way in which the serial number could affect the characteristic under study, this state of affairs may merely be a tribute to his lack of imagination. It cannot be emphasized too strongly that the rationale for confidence statements (vide infra) is completely dependent on the employment of true randomization.[34]
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> * * * * *
>
> "This is achieved by some sort of randomizing process for assigning patients to the two groups * * *
>
> It is worth emphasizing that it is better to build up a well-controlled series in this way even if it has to be done gradually than to get a larger series poorly controlled. Large numbers in themselves are worse than useless if the groups are not comparable, since they encourage confidence in an erroneous opinion.[35]

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Other scientists who have considered this problem emphasize these same principles.[36]

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[34] Lasagna & Meier, "Experimental Design and Statistical Problems," in Waife & Shapiro, *The Clinical Evaluation of New Drugs* 37, 44 (1959).

[35] Marshall & Merrell, *Clinical Therapeutic Trial of a New Drug*, 85 Bull. Hopkins Hosp. 221, 224 (1949).

[36] Martini, *supra*, at 401; Deeley, *The Random Allocation of Patients in Clinical Trials*, 5 Meth. Inform. Med. 100 (April 1966); Armitage, "The Construction of Comparable Groups," in Council for International Organizations of Medical Sciences, *Controlled Clinical Trials—A Symposium* 14 (1960); Truelove, *supra*, at 151; Taber, *supra*, at 89; Goldstein, *Biostatistics: An Introductory Text* 6 (1964); Goldstein, et al., *Principles of*

(5) The plan or protocol must include an outline of the methods of quantitation and observation of the parameters studied in the subjects.

This principle simply requires a statement of the index or indices of drug effect, or the "index of therapeutic accomplishment," used in the study, and a description of how these indices were measured. The selection of a suitable index of effect is a most important part of protocol planning and may be either simple or relatively complicated, depending on the disease entity or symptom being treated.

> The choice of variables to be measured will depend upon the disease. In some, for instance, the status of the heart will be of dominating importance, in others joint swelling and pain, and so on. The methods of measurement must remain unchanged throughout the course of the trial. Any criteria of assessment of the patient's condition must similarly remain unaltered. Clear definitions of methods, criteria, times of measurement, and clinical assessment must be agreed upon before the trial starts. Such methods, criteria and time schedules should be adhered to as closely as possible. Every departure from the rules lowers the efficiency of the trial.
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> In the field of psychopharmacology, where the variables involved make objective measurements either difficult or irrelevant, a scoring system for the evaluation of the symptoms may prove of value. The use of newer techniques and instruments may in time aid quantitative evaluation of psychiatric signs and symptoms.

Drug Action 799 (1968); Nickerson, *The Control of Unknown Variables*, 97 Canad. Med. Assn J. 118–122 (July 15, 1967); Mainland, *Elementary Medical Statistics* ch. II & III (2d ed. 1963); Hill, *The Clinical Trial*, 247 N. Eng. J. Med. 113, 115 (1952); Hill, *Statistical Methods in Clinical and Preventive Medicine* 9, 20 (1962); Doll, *supra*, at 161; Gaddum, *supra*,

It is axiomatic in any trial that the same care and precision in measurement be applied to all groups whether treated with a new drug or not.[37]

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Similarly, we must plan in advance the observations that must be made to measure the changes in the patient that follow the exhibition of the treatment. We must closely consider the advantages and limitations of such objective but isolated measurements as the changes in the sedimentation rate and temperature, and the advantages and limitations of the more subjective clinical assessments of the changes in the "whole" patient. The stress laid upon such observations being made "blind", i.e. without a knowledge of the treatment given to the individual patient, is merely to ensure that the observer can make his assessments without fear of bias, conscious or unconscious, and, equally, without fear of being accused of bias.[38]

* * * * *

When objective measurement of effects is possible, and when pharmacodynamic actions are potent, reproducible, and are not significantly influenced by psychic forces, precise evaluation is relatively simple. Drug actions which must be evaluated in terms of subjective responses, and especially those which are not in themselves impressive, are far more difficult to measure or even estimate. Drug actions on function, which, like blood pressure, have a tendency to wide spontaneous variation or are altered by immediate circumstances, such as tension, position, strain, etc., provide serious problems in assessment.[39]

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[37] World Health Organization, *supra*, at 21.

[38] Hill. *The Clinical Trial*, 190 Practitioner 85, 87 (January 1963).

[39] Modell, *The Sentivity and Validity of Drug Evaluations*. 1 Clin. Pharmacol. Ther. 769, 770 (1960).

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Once the patients are properly allocated to treatment groups, attention must be turned to errors of meaurement. An experiment excellent in all other respects may fail because measurements are made with insufficient care or because of inadequate record-keeping.

If measurements are not carefully made, real differences between drugs may be missed. Randomization and double-blind techniques will prevent the experimenter from frequently claiming differences that are not present. However, they will not help him to control poor precision of measurement. Unbiased but sloppy measurements may lead to the correct assertion that "no significant difference was found."[40]

* * * * *

* * * [a] well-designed trial may fail to provide a clear result because the techniques used for assessment are so prone to error that by their use the effect of the treatment, though real, cannot be detected. If confusion is to be avoided it is necessary for those who undertake clinical trials to be as careful over the choice, description, and execution of the methods they use for diagnosis and assessment as they are over other aspects of the design of their trial.[41]

The proper selection of indices of therapeutic response and the measurement of these indices is of such importance in the clinical trial that whole chapters of books have been devoted to this issue.[42]

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[40] Lasagna & Meier, "Experimental Design and Statistical Problems," in Waife & Shapiro, *The Clinical Evaluation of New Drugs* 37, 45 (1959).

[41] Fletcher, *supra*, at 19. See also Marshall & Merrell, *supra*, at 226; Hill, *The Clinical Trial*, 247 N. Eng. J. Med. 113, 117 (1952).

[42] Feinstein, *supra*, ch. 14: Cox, *supra*, ch. 11 & 12.

(6) *The plan or protocol must include a description of the steps taken to document comparability of variables, such as age, sex, duration of disease and use of drugs other than those being studied.*

Since, as was pointed out above, the object of the controlled clinical trial is to be able to draw a causal connection between any observed difference in response of the treatment groups and the treatments under test, it is desirable to have any other variable which is likely to influence treatment outcome distributed among treatment groups in a relatively equal way. With large treatment groups, simple randomization will usually ensure this, but as treatment groups become smaller, there is a greater likelihood that a variable relevant to treatment outcome may be unequally distributed among treatment groups simply due to the play of chance. To minimize this risk, it is often wise to stratify or pair subjects before randomization for those characteristics likely to influence treatment outcome. If, on examining the treatment groups after a trial, a significant difference in the distribution of some variable is noted, one must consider if this variable is of a nature likely to influence treatment outcome. If so, techniques such as subdivision of cases may be applied to gauge the impact of this variable on treatment outcome.[43]

> The intention in a controlled trial is to provide groups of patients, alike as far as possible, except that they receive different treatments. Before the progress of the groups can legitimately be compared it is important to see that they were initially alike. The analysis must therefore include a section on comparability of groups. On general grounds this should usually show equality in age- and sex-distribution.

[43] Cox, *supra*, at 223.

The frequency of presenting symptoms, duration of illness at the start of treatment, number of previous attacks, and severity, are characteristics which can often come into such comparisons."[44]

* * * * *

If relevant background information on different variables in patients is available, "stratification" of such information may increase specificity of comparisons and conclusions. In other words, the original sample of patients may be sub-divided (stratified) into appropriate and more homogeneous sub-groups, and a random sample withdrawn from each of these for allocation to treatment. The sub-sample may or may not be proportional to the number of units in the sub-group."[45]

* * * * *

The object is to produce two (or more) groups of patients similar in respect to any known or unknown characteristics that may affect the prognosis of their illness but differing in their treatments. When that prognosis may vary considerably between patients of known characteristics, e.g. men compared with women, young people compared with old, patients presenting with fever compared with the afebrile, then it is wise and customary to subdivide the patients on entry to the trial by these characteristics and to make the random allocation within each such subdivision. Thus equality in these characteristics is predetermined.

With the unknown characteristics that may influence prognosis we can, of course, only rely upon the random distribution of the patients to equalize the groups in those respects. This is a reasonable assumption when the numbers involved are not too small and is, indeed, the aim

[44] Knowelden, *supra*, at 157.

[45] World Health Organization, *supra*, at 22.

> of the method. Thus, having first analysed the data to show that in observable characteristics the groups are indeed similar upon entry to the trial, we may with confidence explore the changes that take place in them subsequently and attribute any notable differences to the one known difference between them: i.e. the treatment. For such comparisons between the groups the indices customarily and traditionally used in medicine will be required."[46]

* * * * *

(7) *The plan or protocol must include a description of the methods of recording and analysing the patient response variables studied.*

This requirement, a logical extension of the foregoing principle, stipulates that the methods of measuring patient response shall be specified. The data generated by these measurements must be recorded and analysed, and knowledge of how this was done is vital to any judgment on the significance of the investigator's conclusions. There seems to be no disagreement in the literature as to the importance of this principle, and a vast body of literature exists describing appropriate methods of processing and analysis for particular types of data.

* * * * *

> Before a therapeutic trial is begun, a written statement should be prepared setting out in detail the question(s) being asked, the treatment(s) to be used and the measurements that will be required. This statement should incorporate information about the patients to be admitted and how they will be allocated to the

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[46] Hill, *The Clinical Trial*, 190 Practitioner 85, 88 (January 1963). See also Marshall & Merrell, *supra*, at 225; Hill, *Principles of Medical Statistics* 260 (8th ed. 1966); Armitage, "Statistical Aspects of Clinical Trials," in Zaimis & Elis, *Evaluation of Drugs in Man* 165, 169 (1965).

different treatments. The method of making measurements must be laid down and the times at which they will be made must be specified. In all this the medical statistician should be closely concerned. In some matters laboratory staff should also be consulted, since additional work may be created by tests for toxicity or drug analyses.

Following this statement of the whole project, it will be necessary to construct forms upon which all the data of the trial will be recorded. Care here is of the utmost importance. Attention must be given to such matters as patient identification, the treatment administered to each, and the measurements and clinical assessments that will be made at defined intervals.

Skilful design of this form will save much time both in the recording and in the subsequent analysis of the data. It may be necessary to construct the form so that the data can easily be transferred to punch-cards and sorting machines or to a computer.[47]

* * * * *

In the adoption of other measures of the effect of treatment, detailed planning must as usual play its part. Before the trial is set under way it must be laid down, for example, precisely when and how temperatures will be taken, when full clinical examinations will be made, and what will be specifically recorded, how often and at what intervals X-rays will be taken. Standard record forms must be drawn up, and uniformity in completing them stressed. Unless these rules and regulations are well kept and observed by the clinicians in charge of the trial, many and serious difficulties arise in the final analysis of the results, * * *[48]

* * * * *

[47] World Health Organization, *supra*, at 27.

[48] Hill, *Principles of Medical Statistics*, 259 (8th ed. 1966).

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> The design of patient report forms is largely predicated upon a proper experimental plan. They serve as the backbone of documentation: They are essential for the proper organization, analysis, and interpretation of data, as well as for the collation, storage, and retrieval of information from clinical studies. In our experience, one of the best means to satisfy good experimental design is to devise and prepare a patient report form with practicality and foresight, preferably designing it when the clinical protocol is devised—both become interlocked."

(8) The plan or protocol must include a description of the means of excluding minimizing bias from the observations.

Not only is it important in a controlled trial to avoid bias in the course of setting up the treatment groups to be compared, but it is also important to minimize the introduction of bias which may arise during the course of the experiment due to the preconceptions and expectations of the investigator, observer, and patient. This is usually achieved by the use of "blind" techniques. While physicians have never had any difficulty in accepting the fact that the patient is suggestible, physicians seem to have found it much harder to accept the fact that they themselves are likewise sug-

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[49] Burk & Buday, *Patient Report Forms: Their Design and Use in Drug Evaluation*, 7 Curr. Ther. Res. 422 (July 1965). See also Sutherland, "The Design of Records and Follow-Up," in Council for International Organizations of Medical Sciences, *Controlled Clinical Trials—A Symposium* 151–154 (1960); Knowelden, *supra*, at 155–159; Truelove, *supra*, at 152; Taber, *supra*, ch. 11; Cox, *supra*, ch. 14–16; Lasagna & Meier, "Experimental Design and Statistical Problems," in Waife & Shapiro, *The Clinical Evaluation of New Drugs* 37, 46 (1959); Modell & Houde, *Factors Influencing Clinical Evaluation of Drugs with Special Reference to the Double Blind Technique*, 167 J. Am. Med. Assn. 2190, 2194 (1958; Carr, *supra*, at 313.

gestible, and that observations would be less than objective if the physician's expectations and biases were not taken into account.[50] There are situations in which the injection of bias of this sort into the experiment due to the preconceptions of the patient and observer is quite easy, and others in which it is highly unlikely. In general, the double blind control should be incorporated into the experiment whenever it is feasible, unless there is very good reason to believe that bias on the part of the patient, observer, and investigator cannot affect the outcome.

> Double-blind and single-blind techniques. The expression "double-blind" (sometimes "double-blindfold") is used to describe a trial in which the nature of the treatment being received by a subject at any time is unknown to both subject and observer. This precaution gives protection against the preconceptions and anticipations of both, and is often required to render the trial valid and the data interpretable.
>
> Provision must always be made to enable the observer to find out immediately what the drug is, if it should be in the patient's interest to do so. The double-blind technique, properly conducted, is in no way unethical.
>
> The term "single-blind" refers to a trial in which one participant, usually the subject rather than the observer or investigator, is unaware of the treatment he is receiving at any specific time. Such a control is almost always less satisfactory than the double-blind technique, and the slight gain in convenience hardly compensates for the potential loss of rigour in the study.[51]

* * * * *

[50] Gold, *supra*, at 41.

[51] World Health Organization, *supra*, at 24.

The person of the physician and his medications have been shown to be symbolic forces of considerable potency in the relief of symptoms, the so-called placebo action. In addition, the hopes of the patient and the therapist, as well as any bias either may have with respect to treatment or experiment, also influence response to treatment. These must be reckoned with in all clinical evaluations.

The patient may want to get better to the extent that he is inclined to see good effects after administration of any new medicament. On the other hand, he may find compensations in his illness and wish to preserve his complaints and hence be inclined to see negative pharmacodynamic effects. "Toxic" effects from placebo are described in the literature, the so-called negative placebo action.

The physician's knowledge of the nature of the medicament is exceedingly important, for, regardless of how much he tries, if he knows the identity of the medicament, he may well communicate this information to the patient. The importance of this unconscious (or conscious) communication has been proved by a study by Batterman and Grossman, in which no difference between aspirin and placebo was detected by the patient unless the physician knew whether he was giving one or the other.

The standard and well-documented procedure is not only to use both placebo and drug which are identical in appearance but also to keep both physician and patient ignorant of what is in use at the time of questioning, examination, and prescription, i.e., the double-blind technique. Both placebo and drug not only should look alike but also should be prescribed and administered alike in order to prevent bias of both patient and physician from producing apparent drug actions. To be a real control, the placebo should also closely imitate the test-drug in any incidental effects such as taste, or other

action perceivable by the patient or physician, but it should be independent of the action under question in the test.

This device, however, does not eliminate bias as an element in the method; it merely attempts to deal with it by equalizing its effects, so that unequally distributed bias alone will not fashion the apparently decisive evidence. At this point, it seems appropriate to emphasize that the double-blind technique is merely a control device; for that reason, we shall designate it the double-blind control.[52]

* * * * *

In the above paragraphs it was remarked that imprecise measurements might make it impossible to detect a substantial actual difference between drugs. An even more serious error, however, is to find and declare statistically significant differences that arise from sources other than true drug effects. Most patients with disease want to get better, and most investigators have some sort of prejudice about any given drug—usually in wanting to come up with successful results, but at times in the opposite direction. This enthusiasm (or lack of enthusiasm) must be allowed to diffuse itself out as equally as possible over the medications under study. The major reliance here must be placed on "blind" technique. Usually, this is "double blind," i.e., patient and observer are both unaware of the nature of a particular medication. At times, a "single blind" technique suffices, if the end point to be determined (such as death) is not particularly amenable to overstatement or understatement, or if the patient records the data himself under circumstances in which the experimenter cannot influence him.

Whether the treatments being compared are active drugs or active drugs and placebos, it is

[52] Model & Houde, *supra*, at 2195.

> necessary (for successful deception) to have tablets or capsules or injections that are as indistinguishable in physical appearance as possible. The medications are then designated by code letters or numbers (preferably a different one for each patient) and the code is known only to certain individuals not directly concerned with the performance of the trial. [Lasagna and Meier (32) p. 47 [53]]

* * * * *

Techniques for avoiding bias in the assessment of therapeutic results have been discussed very fully in the scientific literature.[54]

(9) *The plan or protocol must include a precise statement of the nature of the control group against which the effects of the new treatment modality can be prepared.*

There seems to be universal agreement among those conducting clinical trials that a suitable standard of comparison for the test medication is essential if its therapeutic efficacy is to be properly assessed. The nature of this standard of comparison or "control treatment" will vary depending on the kind of information desired concerning the test medication, the nature of the disease entity being studied, and whether

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[53] Lasagna & Meier, *Experimental Design & Statistical Problems "in Waife and Shapiro," the Clinical Evaluation of New Drugs* 37, 47 (1959).

[54] Barber, *supra*, at 27; Beecher, *Measurement of Subjective Responses* (1959); Beecher, *Clinical Impression and Clinical Investigation*, 151 J. Am. Med. Assn 44–45 (1953); Goldstein et al., *Principles of Drug Action* 794 (1968); Goldstein, *Biostatistics: An Introductory Text* 9 (1964); Hill, *The Clinical Trial*, 247 N. Eng. J. Med. 113, 117 (1952); Hollister, *Placebology: Sense and Nonsense*, 2 Curr. Ther. Res. 477–483 (1960); Nickerson, *supra*, at 118–122; Schneiderman, *supra*, at 67; Jaber, *supra*, at 86; Truelove, *supra*, at 153; Van Winkle et al., *supra*, at 960; Gold, *supra*, at 41; Carr, *supra*, at 309; Laurence, *supra*, at 12; Gaddum, *supra*, at 197.

standard medications generally accepted as being efficacious in the particular disease already exist.

For quantifying the therapeutic and toxic effects of a new drug, there are two usual standards of reference. One is the placebo, and the other is the drug (or drugs or other forms of therapy) generally accepted as the best treatment already available. The decision whether to include only the placebo, only a standard drug, or both, will depend on the nature of the disease, the drugs already in use for the disease, the state of the relevant experimental methodology, and the goals of the study. Placebos may be crucial to the interpretation of an investigation in which the performance of a new drug appears similar to, or inferior to, the standard medication. Even here, however, the use of placebo controls is not mandatory; the establishment of dose-response curves for the new and the standard drugs may obviate the need for a placebo and will indeed provide a clearer picture of the status of a new drug than a placebo-controlled experiment with single dose levels of new and old drugs.

The placebo is a control for two types of phenomenon. One, the best known and appreciated, is the effect of suggestibility, personality, attitudes, anticipations and other biases on the part of the patient, investigator or observer. These biases may be in the direction of augmenting the benefit of treatment or of diminishing it, of concealing side-effects or of reporting or displaying ill-effects that are unrelated to treatment.

In addition, the placebo provides a vital control for spontaneous changes in the course of the disease or in the symptoms under study, as well as for events that are independent of the treatments under study. In the absence of a period of study with, or of a group of patients receiving, no treatment of any kind (in-

cluding placebo), it is impossible to determine the relative contribution of spontaneous changes in the disease and other events independent of treatment to the overall placebo "success rate" or "toxicity rate." In most instances, however, this distinction will not be important to the investigator, and the placebo will remain an important tool for distinguishing between a true pharmacological effect and both the psychological effects of taking medication and the fortuitous changes associated with the passage of time.[55]

* * * * *

Concurrent or retrospective controls. In between patient comparisons, the patients in the group receiving the treatment under test and those in the control group are generally best allocated concurrently. By doing this, known and unknown fluctuations in the disease, the environment and the type of patient admitted are more likely to be equally represented in each group.

If patients treated in the past are used as controls, the likelihood that the treated and the control groups will be equivalent is much less.

Concurrent controls are particularly important where the natural history of diseases or symptoms is likely to be inconstant and where changes in the kind of patient to be selected, or in the environment, frequently occur. But where the prognosis is fairly constant, retrospective controls may be acceptable and may, indeed, be the only kind that are ethically permissible.[56]

* * * * *

* * * [O]ne of the most important decisions in planning a study is the selection of preparations to be compared. The classical basis of comparison is an inert lactose placebo, which

[55] World Health Organization, *supra*, at 23.

[56] World Health Organization, *supra*, at 24.

allows determination of whether the test substance has any pharmacodynamic effect in the dose administered. This is sometimes a very important and difficult question to answer, but comparison with a completely inert preparation is often far from ideal * * *

* * * [A]t the present stage in the development of drug therapy, the difference between no therapeutic effect and some effect is often not the most important distinction to make. A more important question may be whether the test drug is less effective, equivalent to or more effective than some similar agent of established therapeutic value. . . . Consequently, it is often desirable to select an agent for comparison which ranks as high as possible in proved therapeutic effectiveness and which is as similar as possible to the test drug in its mechanism of action and in the types of side effects produced.[57]

(10) *The plan or protocol must include a survey of statistical methods used in analysis of the data derived from the subjects.*

With most clinical trials, a formal statistical analysis of differences observed is required to minimize the drawing of conclusions unjustified by the magnitude of differences obtained and the number of subjects studied. Appropriate statistical analysis can also greatly increase the amount of information that can

[57] Nickerson, *supra*, at 120. See also Van Winkle et al., *supra*, at 960; Schneiderman, *supra*, at 68; Armitage, "The Construction of Comparable Groups," in Council for International Organizations of Medical Sciences, *Controlled Clinical Trials—A Symposium* 14–18 (1960); Gaddum, *supra*, at 11; Taber, *supra*, at 85; Gold, *supra;* Hill, *Statistical Methods in Clinical and Preventive Medicine* 3–28 (1962); Goldstein et al., *Principles of Drug Action* 794 (1968); Modell & Houde, *supra*, at 2194; Hill, *The Clinical Trial*, 190 Practitioner 85 (January 1963); Doll, *supra*, at 159.

be extracted from a body of data. There are times when the results of a clinical experiment are so clear-cut that a test of statistical significance is unnecessary, but unfortunately, medications are seldom this startlingly effective. The choice of a method of statistical analysis appropriate to a given experimental design and body of data may be quite difficult, and, except in rather obvious cases, the investigator should justify his choice of statistical methodology in the protocol.

If the experiment has been well designed and conducted and has not run into special difficulties, the statistical analysis should create no problems. However, there are a few basic principles that deserve consideration.

First, the nature of the analysis is entirely dependent on the design of the experiment. (This assertion may seem to be a truism, but it is surprising to see how often it is overlooked. For example, one can find many instances in which a sample of paired observations is analyzed as if the observations were independent.) Any experimenter would do well to be sure he knows how to design, make random allocations for, and analyze the simplest kinds of experimental designs—in particular the completely randomized and the randomized-block designs. If, for some reason, a more complex design is needed, he should seek the advice of a competent statistical consultant. It is true that the complex designs and methods for their analysis are carefully described in a number of texts, but the necessary assumptions are not always clearly set forth and, even when they are, the likelihood that the clinical study in question will not materially violate the assumptions is

better decided jointly by the clinician and the statistician than by either alone.[58]

* * * * *

The planning execution and analysis of a therapeutic trial demand statistical ways of thinking and statistical techniques. If a statistician is involved, as consultant or as one of a team, he should preferably be a medical statistician. He should be able to assist in the design of the trial so that comparisons of the various treatments will be made as precisely and as efficiently as possible and with minimal disturbance from other factors that may influence the clinical response.

Often, however, it is not sufficient for the statistician to be involved solely in the original design of the trial and in the final analysis of its results. During the course of a trial many problems may arise, small or great, that demand immediate attention and, possibly, some modification of the original design. These problems may well have statistical implications and the advice of the statistician should be sought as they arise and not after the event, when it is too late to take action.

In the final analysis of the results, one treatment will be contrasted with another. A formal test of statistical significance may then be required. It is important that the clinical investigator understand the meaning of this test. It tells him how often a difference between two (or more) groups of patients of the observed (or greater) magnitude would have arisen by chance. If the difference is unlikely to have arisen by chance, the investigator is in a posi-

[58] Lasagna & Meier, "Experimental Design and Statistical Problems," in Waife & Shapiro, *The Clinical Evaluation of New Drugs* 37, 55 (1959).

> tion to conclude that it is due to the drug he is testing. The better the design and conduct of the trial, the surer he can be of that conclusion.[59]
>
> * * * * *
>
> The fourth major principle refers to the analysis of data in a sophisticated fashion so that one can answer such important questions as "What are the chances that the observed differences between treatments may have been due to chance alone?" or "How reliable are my estimates of the potency of these drugs?" Let it be emphasized that a flagrant disregard of one or more of the principles previously described usually renders it unnecessary to apply any statistical techniques to the data.[60]
>
> * * * * *
>
> It is well to remember that statistics prove nothing—they are merely a device for establishing the betting odds on the reproducibility of the results by mere chance. Statistical prognostication is always based on the assumption that the data used were worthy of collection; statistical analysis of poor data is tantamount to attempting to make a silk purse out of a sow's ear.[61]

A number of excellent texts are devoted to statistics as applied to medical surveys and experiments and include material both on general statistical concepts relating to the design of medical experiments and on specific tests of statistical significance appropriate for various types of controlled clinical trials.[62] There are

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[59] World Health Organization, *supra*, at 28.

[60] Lasagna, *The Controlled Clinical Trial: Theory and Practice*, 1 J. Chron. Dis. 353, 363 (1955).

[61] Modell & Houde, *supra*, at 2196.

[62] Hill, *Principles of Medical Statistics* (8th ed. 1966; Mainland, *Elementary Medical Statistics* (2d ed. 1963); Goldstein, *Biostatistics: An Introductory Text* (1964).

also symposia and monographs, one or more chapters of which deal with the above points.[63]

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[63] Armitage, "Statistical Aspects of Clinical Trials," in Zaimis & Elis, *Evaluation of Drugs in Man* 165–170 (1965); Armitage, "The Construction of Comparable Groups," in Council for International Organizations of Medical Sciences, *Controlled Clinical Trials—A Symposium* 14–18 (1960); Beecher, *Measurement of Subjective Responses* (1959); Cox, *supra*; Goldstein et al., *Principles of Drug Action* (1968); Hill, *Statistical Methods in Clinical and Preventive Medicine* 3–28 (1962); Hill, "Aims and Ethics," in Council for International Organizations of Medical Sciences, *Controlled Clinical Trials—A Symposium* 3–7 (1960); Schneiderman, *supra;* Taber, *supra;* Truelove, *supra.*

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In the Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-528

CIBA CORPORATION, PETITIONER

v.

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND DR. CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

BRIEF FOR THE RESPONDENTS

OPINIONS BELOW

The opinion of the court of appeals (A. 215) is reported at 463 F. 2d 225. The order of the district court (A. 214) is not reported. The district court did not enter a written opinion.

JURISDICTION

The judgment of the court of appeals (A. 216) was entered on June 5, 1972. By order dated September 1, 1972, Mr. Justice Rehnquist extended the time for filing a petition for a writ of certiorari to October 2, 1972. The petition was filed on that date and was

granted on January 8, 1973 (A. 217).[1] The jurisdiction of this Court rests on 28 U.S.C. 1254(1).

STATUTES INVOLVED

Relevant provisions of the Federal Food, Drug, and Cosmetic Act of 1938, 52 Stat. 1040, as amended, 21 U.S.C. 301 *et seq.*, are set forth in the appendix (A. 475–481).

QUESTION PRESENTED

Whether a manufacturer is entitled to litigate *de novo* in district court the status of his product as a "new drug" when FDA has withdrawn approval of the product's new drug application for failure to establish the product's effectiveness, and the agency determination has been upheld on direct judicial review.

STATEMENT

Petitioner Ciba Corporation ("Ciba") manufactures a drug product, Ritonic Capsules,[2] for which it filed a

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[1] On the same day this Court granted writs of certiorari in four related cases, consolidated them with this one, and allotted a total of three hours of argument. The four other cases are *Weinberger* v. *Hynson, Westcott and Dunning, Incorporated*, No. 72–394; *Hynson, Westcott and Dunning, Incorporated* v. *Weinberger*, No. 72–414; *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72–555; and *USV Pharmaceutical Corporation* v. *Weinberger*, No. 72–666.

[2] "Ritonic Capsules" is a combination of a stimulant (methylphenidate hydrochloride), vitamins and hormones (A. 197). It is a prescription drug recommended "for patients who are losing their drive, alertness, vitality and zest for living because of the natural degenerative changes of advancing years"; and for patients who are "debilitated or depressed by chronic illness, overwork, etc., as well as those recuperating from illness or surgery" (A. 198).

new drug application ("NDA") that became effective in 1959. At that time, the Federal Food, Drug, and Cosmetic Act of 1938 defined a "new drug," in pertinent part, as a drug not generally recognized by qualified experts as safe for its intended uses (Section 201(p)(1), 21 U.S.C. (1958 ed.) 321(p)(1))[3] and provided that such a drug could not be marketed unless an NDA were in effect for it (Section 505(a), 21 U.S.C. (1958 ed.) 355(a)). Under that Act, an NDA for a "new drug" was to become effective if its manufacturer submitted to the Food and Drug Administration ("FDA")[4] with its application adequate proof of the drug's safety (Section 505(b), (c), and (d), 21 U.S.C. (1958 ed.) 355(b), (c), and (d)).[5] The NDA for Ritonic Capsules was permitted to become effective on the basis of the drug's safety.

The 1962 Amendments to the Federal Food, Drug, and Cosmetic Act, among other things, direct the Secretary to withdraw approval for NDAs permitted to

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[3] Relevant provisions of the Federal Food, Drug, and Cosmetic Act of 1938 (21 U.S.C. (1958 ed.) 301 *et seq.*) are set forth at A. 482–484. In order to avoid "new drug" status, a product must also have "been used to a material extent or for a material time" (Section 201(p)(2), A. 483). This portion of the definition is not involved in the issues presented by the instant case.

[4] The Commissioner of Food and Drugs administers the Act pursuant to a delegation of authority by the Secretary of the Department of Health, Education, and Welfare. See our brief in *Weinberger* v. *Bentex Pharmaceutical, Inc.*, No. 72–555, p. 4, n. 5 (hereinafter "Pet. Br. *Bentex*").

[5] The Federal Food, Drug, and Cosmetic Act of 1938, prior to its amendment in 1962, is described more fully in Pet. Br. *Bentex*, pp. 3–5.

become effective prior to 1962, if, after notice and opportunity for hearing, he finds a lack of "substantial evidence" that the drug involved is effective as claimed in its labeling. The statute defines "substantial evidence" to mean "adequate and well-controlled investigations" from which experts could conclude that the drug will have the effect claimed for it. Sections 505 (d) and 505(e)(3), 21 U.S.C. 355(d) and 355(e)(3) (A. 478–479).[6]

1. *The agency proceedings.* Pursuant to FDA's program for implementing the 1962 Amendments,[7] the panel on psychiatric drugs established by the National Academy of Sciences—National Research Council ("NAS–NRC") reviewed the claims made for Ritonic Capsules and found it "ineffective" for each of its claimed indications (A. 196–197). The Commissioner, after review of the NAS–NRC evaluation, also concluded that there was a lack of substantial evidence of Ritonic Capsules' efficacy and accordingly, on September 12, 1969, issued a notice announcing his intention to withdraw its NDA. The notice offered Ciba an opportunity to submit adequate and well-controlled studies bearing on the efficacy of the drug and also stated that withdrawal of approval for the NDA would cause Ritonic Capsules to be a "new drug" for which no NDA is in effect (A. 199–202), thereby making future sale of the drug unlawful.

Ciba responded to the notice by letter dated October 10, 1969 (A. 202–203). It disputed the Commis-

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[6] See Pet. Br. *Bentex*, pp. 14–15.

[7] See *id.*, pp. 16–19.

sioner's conclusion that there was a lack of substantial evidence of Ritonic Capsules' efficacy; submitted "by incorporation by reference" data it had previously submitted to FDA; and reserved "all rights to assert that Ritonic is not a new drug and is not subject to the provisions of Section 505 of the Food, Drug, and Cosmetic Act as amended (21 U.S.C. 355)."

On August 5, 1970, having concluded that the information submitted by Ciba did not provide substantial evidence of the drug's effectiveness, the Commissioner published a notice of opportunity for a hearing on his proposal to withdraw approval for Ritonic Capsules' NDA (A. 203–206). In accordance with the statute and the applicable regulations (21 C.F.R. 130.12(a)(5), 130.14) (A. 487–491),[8] the Commissioner conditioned the hearing on the proffer by Ciba of "a well-organized and full-factual analysis of the clinical and other investigational data [it is] prepared to prove in support of [its] opposition" to the proposed withdrawal (A. 205). Once again the Commissioner announced that withdrawal of approval for Ritonic Capsules' NDA would cause any drug containing the same components with the same claimed uses "to be a new drug for which an approved new-drug application is not in effect" (A. 204) and which therefore could not be marketed lawfully.

By letter dated August 31, 1970, Ciba responded to the notice of opportunity for hearing (A. 206–207). It "elect[ed] to avail itself of the opportunity for a hearing"; contested the Commissioner's authority to

[8] See Pet. Br. *Bentex*, p. 22.

require a statement as to why approval should not be withdrawn as a condition for a hearing; and advised the Commissioner of Ciba's "position that Ritonic Capsules are not now a new drug under the [Act] and that the amendments of 1962 are not applicable to that drug." Ciba's decision to request a hearing, it said, "is made with a reservation of the right to establish these facts in the administrative proceedings, or in judicial proceedings, or both."

Ciba did not file any data to support its request for a hearing or state reasons why approval for its NDA should not be withdrawn. Accordingly, on September 30, 1970, the Commissioner published an order withdrawing approval for Ritonic Capsules' NDA on the ground that there is a lack of substantial evidence that the drug is effective as claimed (A. 207–208).

Ciba petitioned for review of the withdrawal order in the Second Circuit pursuant to Section 505(h) of the Act.[9] On July 16, 1971, the Second Circuit affirmed the withdrawal order, upholding the requirement imposed by the agency's regulations that in a proceeding to withdraw approval for an NDA for lack of "substantial evidence" of effectiveness, the applicant must

[9] Section 505(h), 21 U.S.C. 355 (h), A. 480–481, provides in pertinent part: "An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside."

demonstrate that it has such evidence in order to obtain a full evidentiary hearing. *Ciba-Geigy Corp.* v. *Richardson,* 446 F. 2d 466. Ciba did not seek review in this Court of the Second Circuit's decision.

2. *Proceedings below.* Meanwhile, on September 4, 1970, prior to the issuance of the withdrawal order, Ciba commenced this suit for declaratory and injunctive relief in the federal district court in New Jersey (A. 185–192). It alleged that Ritonic Capsules is not subject to the efficacy requirements of the amended Act by virtue of the exemption provision in Section 107 (c)(4) of the 1962 Amendments,[10] and alternatively that Ritonic Capsules is not now a "new drug" under the amended definition of that term contained in Section 201(p)(1) of the Act (21 U.S.C. 321(p)(1), A. 475) because it is now "generally recognized [by qualified experts] as safe and effective" for its claimed uses (A. 191–192). Ciba asserted that the administrative hearing on the proposal to withdraw approval for Ritonic Capsules' NDA would not encompass those issues, "because the FDA lacks the power to adjudicate [those] issue[s]," but would involve only a resolution of the question whether there is "substantial evidence" of Ritonic Capsules' effectiveness (A. 190, 192). Ciba therefore alleged that it had "exhausted all administrative avenues by which it may seek a determination of its rights on [those] issue[s]" (*ibid.*).

On January 11, 1971, after hearing argument, the district court granted the government's motion to dis-

[10] P.L. 87–781, Section 107(c)(4), 76 Stat. 789, note following 21 U.S.C. (1970 ed.) 321 (A. 482).

miss the complaint for lack of jurisdiction (A. 214). At that time, Ciba's petition to review the order withdrawing approval for its NDA was pending in the Second Circuit. The district court ruled that it did not have jurisdiction to entertain the action under the Declaratory Judgment Act, but that, assuming it did have jurisdiction, it would nevertheless exercise its discretion to dismiss the complaint (*ibid.*).

On appeal, the Third Circuit affirmed, *per curiam* (A. 215–216). In its appeal, Ciba contended that neither the FDA in the withdrawal proceeding nor the court of appeals on direct review of the agency's action had jurisdiction to decide the question whether the product involved is a "new drug" which requires an NDA for lawful marketing. Rather, Ciba argued, the district courts have exclusive jurisdiction to decide that issue, and Ciba was entitled to litigate it in the district court.

The Third Circuit rejected that argument, holding that the agency necessarily is empowered to decide the jurisdictional question as an incident of its power to approve or withdraw approval for NDAs, and that its decision on that issue is reviewable in the court of appeals on direct review of the agency's order. Since the jurisdictional issue was implicitly decided adversely to Ciba by the FDA and the Second Circuit on direct review of FDA's withdrawal order, the Third Circuit concluded that Ciba was not entitled to litigate that question in a separate suit for a declaratory judgment (A. 216).

SUMMARY OF ARGUMENT

This case presents the same basic issue, although in a different context, as *Weinberger* v. *Bentex Pharmaceuticals, Inc.,* No. 72–555: Whether the FDA has jurisdiction in an administrative proceeding to determine whether a drug product is a "new drug" under the definition in Section 201(p) of the Act. The reasons why the FDA has that authority are developed in the government's brief in *Bentex,* and we shall only summarize them in this brief.

This case dramatically illustrates the fallacy of the Fourth Circuit's holding in *Bentex* that the FDA never has jurisdiction to determine the question whether a drug product is a "new drug" under the definition in Section 201(p) of the Act, even in conjunction with the exercise of its regulatory responsibilities under Section 505. Under the *Bentex* holding and the arguments advanced by petitioner in the instant case, the agency must go forward with its regulatory proceedings and the court of appeals with judicial review thereof, while the drug manufacturer retains the right to attempt to establish in *de novo* judicial proceedings that the agency was, after all, simply engaging in an exercise in futility, because the product was not subject to its regulatory powers in the first place.

Such a view is inconsistent with the fundamental scheme established by Congress to regulate the safety and effectiveness of drugs used by the American public, under which administrative regulation will be the primary safeguard, to be supplemented by judicial

enforcement proceedings as a second line of defense. Petitioner's approach would thrust upon the district courts the principal burden of dealing with the complex medical and pharmacological questions underlying the determination of "new drug" status and would entail an extremely wasteful, duplicative approach to drug regulation.

As the court of appeals correctly concluded, FDA's institution of the NDA withdrawal proceeding was itself an assertion that Ritonic Capsules is subject to the Act, and the jurisdictional question was inherent in the proceeding. Petitioner should have contested the "new drug" status of its product before the agency, and, if it believed that the agency applied an incorrect standard in determining that the product was a "new drug" within its regulatory jurisdiction, petitioner should have sought review of that aspect of the agency's determination in its direct appeal to the Second Circuit. Having failed to do so, the finding of "new drug" status became *res judicata* as to petitioner and precludes relitigation in an independent judicial proceeding.

Even if that were not so, petitioner could not prevail in its district court action, since it is undisputed that FDA had the power to determine and did determine that there was a lack of substantial evidence of the effectiveness of Ritonic Capsules. Since, as we argue in our brief in No. 72–414 (the cross-petition in the *Hynson* case), a drug could not be generally recognized as effective if FDA has found that there is a lack of substantial evidence of effectiveness, FDA's

finding to this effect in the administrative proceeding was binding on petitioner and under principles of collateral estoppel precludes it from arguing that its product is not a "new drug."

ARGUMENT

CIBA IS NOT ENTITLED TO A DE NOVO JUDICIAL DETERMINATION OF ITS PRODUCT'S "NEW DRUG" STATUS

Ciba claims entitlement to *de novo* consideration by the district court of Ritonic's "new drug" status on the theory that the issue presented is one beyond the power of FDA to determine administratively, so that the NDA withdrawal proceeding and the subsequent direct judicial review thereof would not have foreclosed new litigation of the "new drug" question.[11] The underlying issue in this case is thus whether FDA ever has authority to determine administratively whether a product is a "new drug" requiring an approved NDA for lawful marketing.

The same issue is presented in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72–555,[12] in which the

[11] Even if Ciba were correct in its jurisdictional argument, however, the district court rightly dismissed its declaratory judgment action. As we indicate at pp. 18–20, *infra*, and discuss at greater length in our brief in No. 72–414, the finding that Ritonic fails to satisfy the effectiveness requirements of Section 505 precludes a finding of "not new drug" status under Section 201(p). Ciba's action therefore must fail under the doctrine of collateral estoppel.

[12] This issue is presented by cross-petitioner Hynson, Westcott and Dunning in No. 72–414. It has aligned itself with the government on this question, arguing that FDA has the authority to determine whether the drug involved in that case requires an NDA for lawful marketing (Brief for Cross-Petitioner in No. 72–414, pp. 17–20).

Fourth Circuit ruled that the FDA may never make that jurisdictional determination administratively. In our brief in *Bentex*, we have shown that the decision denying to FDA the power to determine in its own proceedings the coverage of the Act it administers is inconsistent with the scheme of the Act and would seriously impair FDA's ability to carry out its congressionally assigned responsibility to remove from the market drugs not shown to be effective (Pet. Br. *Bentex*, pp. 34–38, 40–47). The brief also shows why the premises upon which the Fourth Circuit based its *Bentex* decision are erroneous (*id.* at 47–57).

Petitioner Ciba advances essentially the same arguments, to support its contention that the district court is the sole forum in which the "new drug" status of its product may be litigated, as those relied on by the Fourth Circuit in *Bentex*. Since the Court already has before it our argument on these issues, as presented in our brief in *Bentex*, we shall simply summarize them briefly here.

1. *FDA's authority to determine the coverage of the Act is implicit in the statutory scheme.* The Act confers broad administrative responsibilities on the FDA to protect the public by screening all "new drugs" for safety and effectiveness prior to marketing and by maintaining a continuous review of "new drugs" on the market to assure that the agency's initial determination respecting safety and effectiveness conforms to developing medical knowledge and experience. Section 505, 21 U.S.C. 355, A. 477–480. In addition to the administrative responsibility to approve or withdraw

approval for the marketing of new drugs expressly conferred by Section 505, the Act empowers FDA to promulgate regulations (Section 701(a), 21 U.S.C. 371(a)) and conduct investigations (Section 702(a), 21 U.S.C. 372(a)) to carry out the purposes of the Act. The exercise by FDA of these regulatory functions serves as the primary public safeguard against the marketing of unsafe and ineffective drugs. Implicit in the grant of these broad regulatory powers is the power to decide the question on which the FDA's regulatory responsibility turns: Whether the product involved is a "new drug" for which approval is necessary under Section 505.

Section 201(p)(1) defines "new drug" as "[a]ny drug * * * the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof * * *." This definition suggests a determination of technical and scientific questions by experts. It requires a consideration and disposition of issues substantially similar to the isues involved in an agency proceeding for approval or withdrawal of approval of an NDA under Section 505 (see Pet. Br. *Bentex,* pp. 55–57). Resolution of the question of the agency's jurisdiction, which turns on a proper assessment of technical and scientific factual considerations, is therefore a function for which the agency is particularly well-suited.

Thus, the absence of an express grant of power authorizing the agency to determine the coverage of the Act it administers, upon which Ciba (Br. 8) and the *Bentex* opinion (see A. 266) rely, is not dispositive. Just as "[a]uthority to investigate the existence of violations * * * include[s] authority to investigate coverage" (*Oklahoma Press Pub. Co.* v. *Walling*, 327 U.S. 186, 210–211, n. 47), authority to grant, refuse, or withdraw marketing approval necessarily includes authority to determine the threshold question of coverage—whether the product involved is a "new drug" which requires agency approval. See Pet. Br. *Bentex*, pp. 57–60. Indeed, agencies routinely determine the coverage of the statutes they administer, even though the statutes themselves rarely confer explicit authority to do so.

2. *The district court's jurisdiction under the enforcement provisions of the Act does not bar FDA from determining the coverage of the Act.* The Act prohibits, among other things, the sale in commerce of any article in violation of Section 505's requirement of an NDA approved by the agency after administrative consideration. Section 301(d), 21 U.S.C. 331(d), A. 475. It prescribes civil injunction proceedings, criminal penalties, and *in rem* seizure and condemnation to give effect to this and other prohibitions. Sections 302(a), 303, 304, A. 475–477. These judicial enforcement provisions constitute a second line of defense backing up the administrative system of marketing approval established by the Act. They are designed to complement, rather than displace, the administrative approval scheme.

Petitioner's construction of the Act, which provides for mutually exclusive forums for regulating new drugs—one judicial, the other administrative—is both unnecessary and impractical. That the district courts may determine *de novo* in enforcement proceedings whether a product is a "new drug," at least where there has been no formal administrative determination of that issue, does not mean that the agency is therefore powerless to determine its own jurisdiction in the proceedings it conducts.

The impractical consequences of the dual system of regulation urged by petitioner are apparent. It would make the district courts, rather than the agency, the principal forum for determining in all instances whether a product is a "new drug" subject to the administrative clearance and review provisions of Section 505 of the Act. It would thus transfer to the district courts sole responsibility to resolve the often complex questions upon which the definition of "new drug" turns—questions which the expert agency is inherently well suited to resolve.[13]

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[13] Petitioner asserts (Br. 10) that resolution of the question whether a product is a "new drug" (*i.e.*, whether it is generally recognized by experts as safe and effective) involves only a determination of the consensus among doctors, which is "readily within the competence of the courts." In the district court, however, petitioner asserted that a determination of the "new drug" question would involve the testimony of "many experts," and "a great factual investigation and presentation [to the] trier of the facts * * *" (A. 211). This submission reinforces our position that it is the agency in the first instance which should resolve such factual questions peculiarly within its competence.

The necessity for a two-step procedure—an agency proceeding to determine whether NDA approval should be withdrawn and a judicial proceeding to determine whether the NDA was after all required—would inordinately protract FDA's efforts to remove from the market drugs not shown to be effective. Both questions can be and should be decided in a single proceeding. Familiar principles require manufacturers in petitioner's position to raise their objections to the agency's proceeding during that proceeding, instead of "reserving" those objections for *de novo* judicial consideration. See *Myers* v. *Bethlehem Corp.*, 303 U.S. 41.

Petitioner suggests (Br. 11–12) that the agency's failure to raise in the administrative withdrawal proceedings the question whether Ritonic Capsules is a "new drug" shows that petitioner was foreclosed from presenting that issue to the agency for resolution. On the contrary, as the court below observed (A. 216), the institution of the withdrawal proceedings was itself an assertion that Ritonic Capsules is subject to the Act, and the jurisdictional question was therefore inherent in that proceeding. Indeed, petitioner's careful attempt to "reserve" the jurisdictional issue (A. 203, 206–207) (*i.e.*, withhold it from the agency) indicates that petitioner was of a similar view.[14]

[14] The absence of formal agency regulations setting forth the manner in which jurisdictional questions may be raised did not preclude petitioner from raising the issue. Nor does it indicate that the agency considers itself powerless to determine its own jurisdiction. If petitioner had serious doubts as to whether the agency would entertain petitioner's jurisdictional claims, it should have raised the question before the agency, rather than attempting to reserve it.

Even were petitioner justified in supposing that the agency would have refused to consider its "new drug" contentions—contentions that FDA deems insupportable in the absence of "substantial evidence" of drug effectiveness—its proper remedy was to challenge the correctness of FDA's approach on direct judicial review.[15] Having failed to do so, Ciba is not free to relitigate it in an independent proceeding. See cases cited at note 17, *infra*; cf. *Marine Terminal Assn.* v. *Rederi. Transatlantic*, 400 U.S. 62, 72.

3. *Judicial review of the agency's "new drug" determination is available.* Section 505(h) of the Act (21 U.S.C. 355(h), A. 480–481) provides for direct review in the courts of appeals of an agency order denying or withdrawing approval for an NDA, and petitioner invoked that provision to obtain review in the Second Circuit of the order withdrawing approval for Ritonic Capsules' NDA. In urging that Section 505(h) precludes a court of appeals from reviewing an agency finding that a product is a "new drug," we believe petitioner misreads the statute. Section 505(h) authorizes appeals from certain kinds of orders; it does not, as petitioner suggests (Br. 9), confer jurisdiction on the courts of appeals in terms of particular issues.

The only limitation imposed by Section 505(h) on the issues a court of appeals may decide on direct review is that the issue must have been raised before the agency: "No objection to the order of the Secretary

[15] This was the course followed by Hynson, Westcott & Dunning, which now has before this Court the issue of the correctness of FDA's disposition of its "not new drug" contentions in No. 72-414.

shall be considered by the court [of appeals] unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do." [16]

4. *Petitioner's suit for declaratory relief was properly dismissed.* Petitioner had the opportunity to litigate the "new drug" issue in the administrative proceeding to which it was a party and in which it participated, and it also had the right to judicial review in the court of appeals of the adverse agency determination of that issue. Its failure to raise that issue, indeed its affirmative attempt to carve it out of the administrative proceeding, precludes petitioner from litigating the "new drug" issue in another proceeding, whether it is a declaratory judgment action or an enforcement suit.[17]

5. *Even if petitioner were correct in its jurisdictional argument, it would be barred from relief by collateral estoppel.* It is not disputed that FDA had jurisdiction to consider, and did consider and pass upon, the question whether "there is a lack of substantial evidence that [Ritonic Capsules] will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof," the standard for with-

[16] Where, as in *Bentex*, the agency's "new drug" determination is not reviewable in the courts of appeals pursuant to Section 505(h), it is reviewable in the district courts under the Administrative Procedure Act. See, Pet. Br. *Bentex*, pp. 51-53.

[17] See, *e.g.*, *United States* v. *Ruzicka*, 329 U.S. 287; *Yakus* v. *United States*, 321 U.S. 414, 444-446; cf. *McGee* v. *United States*, 402 U.S. 479.

drawal of approval set forth in Section 505(e)(3). The agency found that there is a lack of substantial evidence of effectiveness, and this finding was affirmed by the Second Circuit. The doctrine of collateral estoppel bars petitioner from relitigating the question in another proceeding.

It is the government's position that a drug that has been determined not to meet either the safety or the effectiveness standards of Section 505 is thereby *a fortiori* a "new drug" under Section 201(p). This is so because, in the absence of scientifically acceptable evidence of safety or effectiveness of the quality and quantity prescribed by Congress for approval of new drug applications, the "experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs," on whose judgment the application of the "new drug" definition expressly depends, could not recognize the drug's safety and effectiveness. Any contrary position would lead to an anomalous situation in which the Act would leave drugs that the expert administrative agency had determined to be unsafe or ineffective unregulated because of judgments based on criteria for evaluation which Congress has expressly rejected.

If the Court agrees with our position, set forth at greater length in our brief in No. 72-414, that a drug must, at a minimum, be able to satisfy the safety and effectiveness criteria of Section 505 in order to attain "not new drug" status under Section 201(p), the conclusion of FDA in the withdrawal proceedings that there is a lack of substantial evidence of Ritonic

Capsules' effectiveness, which is binding on Ci through collateral estoppel, precludes relief to Ci in the declaratory judgment proceeding. See *Unite States* v. *Utah Constr. Co.*, 384 U.S. 394, 422; *Mari Terminal Assn.* v. *Rederi Transatlantic, supra*, 400 U. at 72; *Restatement of Judgments* §§ 68, 69 (1942).

CONCLUSION

For the foregoing reasons and the reasons advanced in our brief in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72–555, the judgment of the court o appeals should be affirmed.

Respectfully submitted.

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(2) the criteria on which approval or disapproval of the application shall be based, none of which relates to the question of whether the drug is "new"; and 9

(3) the criteria on which withdrawal of approval shall be based; and these require, on the basis of new adverse information, withdrawal of approval of an application for a drug not regarded as "new". 11

B. The applicant is entitled to a ruling on its application, even though the FDA does not consider the drug as "new". 13

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(2) No power is given the FDA to refuse an application on the ground that the drug is not "new". 13

(3) Advisory opinions that a drug is not "new" may be and have been withdrawn. 13

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Speech of Mr. Peter Barton Hutt,
September 4, 1969 13

IN THE
Supreme Court of The United States

No. 72-555

October Term, 1972

CASPAR W. WEINBERGER, Secretary of Health, Education, and Welfare, and CHARLES C. EDWARDS, Commissioner of Food and Drugs, *Petitioners*

v.

BENTEX PHARMACEUTICALS, INC., ET AL.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

BRIEF FOR RESPONDENTS

OPINIONS BELOW, JURISDICTION, QUESTIONS PRESENTED AND STATUTES INVOLVED

The respondents adopt the petitioners' statements in regard to the foregoing.

STATEMENT

Certain matters have already been established by the briefs before the Court submitted in the companion cases of *Weinberger v. Hynson, Wescott and Dunning, Inc.*, No. 72-394; *Hynson, Wescott and Dunning, Inc. v. Weinberger*, No. 72-414 (Cross-petition); *CIBA Corporation v. Weinberger*, No. 72-

528; and *USV Pharmaceutical Corporation v. Weinberger*, No. 72-666.

The thorough and scholarly brief submitted in the *USV* case (No. 72-666) demonstrates, as was already conceded by the Food and Drug Administration, that heretofore the approval of a new drug application has been considered personal to the applicant (Petitioners' brief in such case, pgs. 32-51).

The clear distinction between the evidence relevant to approval of a new drug application and the evidence relevant to the determination of the applicability of the definition of a new drug has been emphasized in the *Hynson* brief (No. 72-414) at pages 25-28, and in the *CIBA* brief (No. 72-528) at page 10.

The implications of longstanding agency practice has been reviewed in the *CIBA* brief (No. 72-528) at pages 12 and 13, and in the USV brief (No. 72-666) at pages 32 and 38.

The preceding briefs have discussed the history of the Federal Food, Drug and Cosmetic Act. All have given their exposition of the plan of the Act.

The petitioners seek in some fashion to create a right of administrative adjudicatory determination as to whether a drug is "new" based upon the responsibility of the agency to pass on new drug applications under Section 505 of the Act. It will be shown in this brief that the approval, disapproval or withdrawal of approval of a new drug application, under Section 505 of the Act, has nothing to do with whether a drug is "new" or "old", and that to interject that question would violate the express provisions of Section 505.

When it is realized that Section 505 of the Act confers no jurisdiction on the Secretary to adjudicate the applicability of the "new drug" definition to any product, it then becomes obvious that the Secretary has no jurisdiction to make binding administrative adjudications of the "new", "old", or "grandfathered" status of any drug. There is, in the Act, no distinction between the enforcement powers given the Secretary as to the sale of an unapproved new drug, and the enforcement powers

created regarding any other prohibitions of the Act. Jurisdiction of all these issues is placed solely in the District Court by the express provisions of the Act.

Beyond the argument which follows the respondents, in preliminary statement, wish to make these points:

(1) It is no disgrace to be a "me-too" drug.

(2) The word "ineffective", as used by the Food and Drug Administration, does not mean what it seems to mean.

(3) The Courts have no need to fear increased litigation as a result of upholding the opinion of the court of appeals in this case.

(1)

Throughout the petitioners' brief there is the implication that a "me-too" product is somehow tainted.

If, during the period of 1938 to 1962, a drug had become generally recognized as safe, everyone had a right to produce it, if no patent existed. Such competition is desirable. It leads to lower prices for drugs. Drug prices were a major concern of the hearings held by Senator Kefauver in connection with the 1962 Amendments, and are still a major concern.

These competing products have the right to an independent life. They are not tied to the apron string of some one else's new drug application. The "pioneer' company may not have chosen to defend its product in hearings for withdrawal of its original new drug application. That application was completely personal to it and was not generic. Frequently such lack of defense indicates nothing more than that the revenue produced by the product in the hands of its original sponsor did not justify the expense of defending it.

Where the proponent of a competing product believes that it can prove that the product is not a "new" drug it is entitled to its own, independent right to do so.

(2)

Throughout the petitioners' brief is the word "ineffective". Generally this word means nothing more than that the

holder of an approved new drug application did not choose to submit evidence of effectiveness to the NAS/NRC review boards. The term does not imply that the drugs in question do not in fact have the effect claimed. The term only implies that evidence of effectiveness satisfactory to the review boards was not submitted for some reason.

The phrase "ineffective" thus generally refers to the failure of a particular applicant to meet or to attempt to meet a specific burden of proof with respect to its own product.

The use of the word "ineffective" must thus not be allowed to exercise the emotional impact carried by its lay meaning.

(3)

Throughout the petitioners' brief there is the repeated implication that a decision against its position will result in a flood of litigation.

The pharmaceutical industry is one of the great responsible American industries. Despite the presence of the Food and Drug Administration it is largely self-regulated and selfdisciplined. It is noteworthy how few cases have developed into serious litigation. Throughout the history of the Act there has been only a thin trickle of decided cases. Many of these cases involve fringe elements of the industry: food fads, strange curative machines, and cure-alls.

In normal course industry promptly and voluntarily discontinues sales of any product concerning which a question has been raised, and voluntarily recalls outstanding stocks. The inherent damage to the reputation of a firm arising from the publicity of a seizure, the desire to maintain friendly relations with the agency, the expense and risk of litigation, all contribute to make defense of a product a course of last resort. Honest recognition of the facts and the sense of public responsibility inherent in most members of industry, combined with the other considerations named, prohibit defense of an indefensible product.

The law as stated in the court below is, we submit, the law as it has always been understood by the industry and by

the agency in accordance with its longstanding practice. This Court's decision in affirmance will not add to the small volume of litigation.

ARGUMENT

INTRODUCTION AND SUMMARY

The provisions of Section 505 of the Act, pertaining to the approval, disapproval or withdrawal of approval of a new drug application, are directed solely to an application voluntarily filed "by any person" with the Food and Drug Administration.

The criteria for action upon such application are precisely defined by the Act. An application may neither be refused nor withdrawn because the agency regards it as unnecessary; nor may the directives of the Act as to when to refuse or to withdraw approval of an application be ignored by the agency on the ground that the drug so covered is no longer "new".

The Act defines circumstances which require approval of an application to be withdrawn despite general recognition of the safety and effectiveness of the product, when newly discovered and undisseminated adverse evidence becomes known to the agency.

The jurisdiction of the agency under Section 505 is not a "threshold question", nor is the agency called upon to determine its own jurisdiction. Its jurisdiction is created by the application. When that is filed the agency has jurisdiction of that application, filed by the applicant. Nothing in the language of Section 505 requires, allows or suggests that the agency is to decide, pursuant to its duties thereunder, whether a drug is "new".

The test of whether a drug is "new" is entirely different from the criteria of approval specified in Section 505.

The test of whether a drug is new has been recognized by many decisions to be its reputation among qualified experts, as is required by the definition provided by Congress in Section 201 (p) of the Act. The criteria of Section 505 are based on the extent of specific and concrete scientific

evidence in support of the drug submitted by the applicant, and relate to actual safety and effectiveness as shown by that evidence.

The criteria of Section 505 may be met in the absence of general recognition of the safety and effectiveness of a drug among the scientific community. Indeed, the Section was designed to allow marketing of newly developed products, which have not yet achieved such recognition. On the other hand, failure of an applicant to sumbit the required proof of safety and effectiveness under Section 505 (d) is no indication that such proof does not exist or that the drug is not generally recognized as safe and effective.

Congress deferred to the expertise of the agency in the evaluation of the scientific proof of the safety and efficacy of unknown products. It placed in the hands of the District Court, with the burden of proof upon the agency, the opinion issue of general recognition which determines whether a drug is "new".

During the thirty-four years of the existence of the Act few cases have been seriously litigated. Circumstances exist which discourage such litigation, in the absence of arbitrary action by the agency.

The innovations now sought by the agency as to its jurisdiction are more likely to cause delay, confusion and litigation than will continued, orderly enforcement under the law and practices heretofore existing.

I. THE TESTS OF WHETHER A DRUG IS "NEW" OR "GRANDFATHERED" ARE DISTINCT FROM THE CRITERIA ON WHICH ACTION ON A NEW DRUG APPLICATION IS BASED.

A. *The Courts have repeatedly recognized the distinction between scientific evidence of safety and effectiveness and the "general recognition" test embraced in the definition of a "new" drug under Section* 201 (p).

The distinction between the tests applicable to "new drug

definition" (201 [p]) and the criteria of Section 505 relating to approval, etc., of a new drug application has been treated in the cross petitioner's brief in the case of *Hynson, Westcott & Dunning, Inc. cross-petitioner v. Richardson, et al.*, No. 72-414, pp. 25-28, and at page 10 of the petitioner's brief in the case of *CIBA Corporation v. Richardson, et al.*, No. 72-528.

As is demonstrated by the argument in those briefs, with which the respondents concur, the application of Section 201 (p) to a drug requires only the determination of the consensus of competent medical opinion.

The evidence to support a new drug application is evidence provided by tests and results.

The statement by the petitioners in their brief, pages 55-57, that the issues are one and the same is an inadmissible repudiation of well established principles enunciated by the Federal courts.

> See e. g., *Merritt Corp. v. Folsom*, 165 F. Supp. 418 (D.D.C. 1958); *U. S. v.* 345 *Bulk Cartons . . . "Trim Reducing Aid Cigarettes"*, 178 F. Supp. 847 (D.N.J. 1959); *U. S. v. An Article of Drug . . . "Quinaglute,"* 268 F. Supp. 245 (E.D. Mo. 1967); *U. S. v. Articles of Drug . . . "Quick-O-Ver,"* 274 F. Supp. 443, 445-46 (D.Md. 1967); *U. S. v. An Article of Drug . . . "Line Away"*, 284 F. Supp. 107 (D.Del. 1968) affirmed other grounds 415 F. 2d 369 (3rd Cir. 1969); *U. S. v. 7 Cartons . . . "Ferro-Lac"*, 293 F. Supp. 660 (S.D. Ill. 1968) affirmed 424 F. 2d 1364 (7th Cir. 1970); *U. S. v. An Article of Drug . . . "Furestrol"*, 294 F. Supp. 1307 (D.Ga. 1969) affirmed 415 F. 2d 390 (5th Cir. 1969); *U. S. v. An Article of Drug . . . "Excedrin P. M."*, F. Supp. , CCH, Food Drug and Cosmetic Law Reporter, ¶ 40,486 (E.D.N.Y. 1971); *U. S. v. An Article of Drug . . . "Bentex Ulcerine," etc.*, F. Supp. , (D. Texas 1972), affirmed F.2d , CCH, Food Drug and Cosmetic Law Reporter ¶ 40,771 (5th Cir. 1972).

B. *Agency determination of the extent of general recognition is particularly subject to administrative bias, and industry needs the protection of the Courts.*

Where issues exist as to the application of Section 201 (p) to a drug an agency adjudication would be subject to bias, particularly unconscious bias.

The determination will rest upon the credence and weight to be given to conflicting expert testimony – not as to matters of fact but as to the existence or non-existence among the expert community of general recognition of the safety and effectiveness of a drug.

In determining questions of credence and weight as applying to the determination of a nebulous consensus, or lack thereof, the testimony of agency witnesses, or of witnesses already familiar to the hearing examiner would only by heroic effort on the part of the examiner be reviewed with truly judicial objectivity and perspective.

Errors arising from unconscious bias in giving weight and credibility to conflicting opinions are almost incapable of correction at the appellate level. If ever there were a case where the protection of the Federal judiciary is needed at the trial level, the "new drug" question is that case.

II. THE ISSUE OF WHETHER A DRUG IS "NEW" IS NOT MATERIAL TO THE APPROVAL, DISAPPROVAL OR WITHDRAWAL OF APPROVAL OF A NEW DRUG APPLICATION UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT.

A(1). *The Act exactly specifies the information to be submitted, none of which relates to the question of whether the drug is "new".*

Section 505 (b) of the Act exactly specifies the information to be submitted as part of a new drug application. It states:

> "Such person shall submit to the Secretary as a part of the application

(1) full reports of investigations which have been made to show whether or not such drug is safe for use, and whether such drug is effective in use;

(2) a full list of the articles used as components of such drug;

(3) a full statement of the composition of such drug;

(4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

(5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and

(6) specimens of the labeling proposed to be used for such drug."

These provisions neither require nor suggest that evidence be submitted as to the general recognition of the safety and effectiveness of the drug among the scientific community ("new" drug definition, Section 201 (p) of the Act; J. A. 475). Nor do they require or suggest that evidence be submitted for determination of the "grandfathered" status of the drug. (Section 107 (c) of *Public Law*, 87-781, 76 Stat. 788-789: J.A. 481, 482).

The information required in the application is designed to allow determination of whether the application should be approved. It is not provided that an application may be used to secure an exemption from approval.

A(2). ***The Act exactly specifies the criteria on which approval or disapproval of the application shall be based, none of which relate to the question of whether the drug is "new".***

Section 505 (d) of the Act exactly specifies the criteria on which approval or disapproval shall be based.

It states:

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of ade-

quate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labelling or proposed labeling thereof.

Provisions 1, 2, 3 and 4, quoted above, require the submission by the applicant of test results and of manufacturing methods.

Provisions 5, 6 and 7 permit the Secretary to *deny* the application based upon other information known to him, not furnished by the applicant, indicating that he should *not* approve the drug. The Secretary is not authorized under any of the provisions of Section 505 (d) to *approve* an application on any basis other than material furnished by the applicant. Only in the disapproval of an application may the Secretary take into account information from other sources.

No provision of 505 (d) authorizes the approval of a new drug application by the Secretary on the ground that the drug is not "new"; nor is there any provision authorizing disapproval of an application on such ground.

It is not material to the criteria prescribed for approval whether the drug is or is not a "new" drug.

A(3) *The Act exactly specifies the criteria on which withdrawal of approval shall be based; and these require, on the basis of new adverse information, withdrawal of approval of an application for a drug not regarded as "new".*

The Act exactly specifies the criteria for withdrawal of approval of a new drug application.

It states:

(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw ap-

proval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with th evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact:

None of the provisions of Section 505 (e) suggests that the Secretary may withdraw approval of an application on the ground that the drug is no longer "new". Nor do these provisions suggest that the Secretary may refrain from withdrawing approval if required to do so under the terms of the Section on the ground that the drug is no longer "new".

In fact, the withdrawal provisions contemplate that a drug already approved, and now generally recognized as safe and effective, may as the result of tests by new methods prove to be unsafe. The fact that unsuspected side effects may exist with respect to accepted products has long been emphasized by the agency.

Section 505 (e) does not suggest that the agency, in a withdrawal proceeding, may consider whether the drug is or is not still a "new" drug.

B. *The applicant is entitled to a ruling on its application, even though the FDA does not consider the drug as "new".*

(1) *The decision to file an application belongs to the applicant alone.*

The decision to apply for approval of a new drug application is up to the applicant. No procedure exists to compel him to do so, nor does procedure exist to deny him that right.

Attention was called in the petitioners' brief in *USV Pharmaceutical Corp. v. Weinberger, et al.* (No. 72-666) to a speech by Peter Barton Hutt, present Assistant General Counsel for the Food and Drug Administration. In that speech, presented at the Annual Convention of the Federal Bar Association, Miami, Florida, Sept 4, 1969, Mr. Hutt stated:

> 'The third, and final, general principle is that it is the primary and initial responsibility of the manufacturer of a product to determine the proper classification of his product, and to make certain that it meets all applicable legal requirements. It is in no instance necessary, and in most instances inadvisable, to ask the Food and Drug Administration for its opinion on the proper classification of the product. • • • It is • • • usually perferable for the manufacturer to exercise the obligation of proper classification given to him by the statute, rather than abdicating that responsibility to the Government.'

B(2) *No power is given the FDA to refuse an application on the ground that the drug is not "new".*

B(3) *Advisory opinions that a drug is not "new" may be and have been withdrawn.*

B(4) *Such advisory opinions are not binding nor are they protection against prosecution or other enforcement action initiated by third parties.*

No authority is vested in the Secretary to refuse a new drug application on the ground that it is not new.

There is now a regulation under which the agency offers advisory opinions as to whether drugs require a new drug application (36 FR 3372, J. A. 247-250). Such advisory opinions are not binding.

Prosecution or other enforcement proceedings by the agency, or by a United States Attorney, or derivatively by a consumer group (as in *American Public Health Association v. Veneman*, DDC, Civ. Action No. 1847-70, decided August 23, 1972) are not precluded by the existence of an advisory opinion. *Davis: Administrative Law Treatise* ¶4.09, Vol. 1, pages 265-267; *Nichols & Co. v. Secretary of Agriculture*, 131 F. 2d 651, 659; *SEC v. Torr*, 22 F. Supp. 602-612; *James Couzens*, 11 BTA 1040.

Advisory opinions may be and have been suddenly withdrawn. As admitted in petitioners' brief:

> "On May 28, 1968, the agency, by formal statement of policy premised on the need for full implementation of the NAS/NRC findings, revoked all opinions previously given to the effect that an article is 'no longer a new drug'."
>
> (Petitioners' brief, page 21)

Accordingly an applicant may have good reason to insist that the agency pass upon and approve its new drug application, even though there is an advisory opinion that none is required.

The applicant has an absolute right under Section 505 to submit its application for approval, and to obtain approval if the application meets the criteria of 505 (d).

The agency is given no authority to refuse an application nor to disapprove it on the ground that the drug is not "new".

The question of the "newness" of a drug is never before the agency for decision under Section 505. Its jurisdiction is invoked solely by the filing of an application, and by the

filing of that application the exercise of its jurisdiction is also commanded.

C. *The Drug Amendments Act of* 1962 *conferred no new jurisdiction on the FDA to determine the newness of a drug, but merely modified the new drug definition and the criteria for approval, disapproval or withdrawal of approval of a new drug application.*

The Drug Amendments Act of 1962, and the efficacy review conducted under contract with the NAS/NRC, have no relevancy at all to the question of the agency's jurisdiction to adjudicate, so as to bind any private person, the question of whether a drug is "new".

The 1962 amendment of Section 505 added the requirement that a new drug application be supported by "substantial evidence" of effectiveness. The jurisdiction of the agency to approve, disapprove or withdraw approval of a new drug application was unchanged. The efficacy requirement was simply added to the criteria for such action.

The 1962 Amendments, while adding to the labors of the Secretary, did not add to his jurisdiction under Section 505. That jurisdiction remained limited to the approval, disapproval or withdrawal of approval, upon exactly prescribed criteria, of new drug applications submitted to the agency.

D. *The restricted rights of appeal under Section* 505 *of the Act are additional evidence that the Secretary is not invested with jurisdiction by that Section to determine whether a drug is "new".*

The court of appeals did not hold, as asserted by the petitioners, "that the agency should not be held to have the power to adjudicate 'new drug' status because its determination would not be judicially reviewable."
(Petitioners' brief, page 47)

Instead it held that the absence of provision for appeal from a decision whether a drug is "new" strongly suggests the intended absence of the power to make that decision.

The court of appeals held:

> "It is not to be assumed that the Act confers an adjudicatory right on the Secretary from which no judicial review, however limited, is provided or allowed." (J. A. 268)

As authority for the absence of the right of appeal from a decision on the new drug issue when promulgated under Section 505 the court of appeals cited *Turkel v. FDA, et al.*, 334 F. 2d 844, and, more importantly, the express language of the Act.

In the *Turkel* case, *supra*, it was held that refusal by the Secretary to grant exemption from Section 505 under the investigative drug section (505 [i]) was not appealable.

At Section 505 (h) the Act provides:

> "An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section."

No authorization for appeal is provided from any other action by the Secretary which he may lawfully take under Section 505.

There is no appeal from the refusal of the Secretary under an imagined authority to exempt a product as "not a new drug". There is no provision for appeal from the refusal of the Secretary to withdraw approval of an application on the grounds that it is no longer necessary.

Unlike the specialized and technical judgment as to whether a new and unapproved product should be exempt for investigational use only, the question of whether a drug is "new" under Section 201 (p) has routinely been decided by the courts. The agency acknowledges that it may properly be so decided in enforcement proceedings (petitioners' brief, page 57, footnote 82).

The fact that an issue amenable to Court decision is unappealable when decided by the agency under Section 505 is persuasive evidence that Congress never intended to provide that the agency decide that issue.

E. *The lack of any procedure or regulations established by the agency to adjudicate whether a drug is "new" is evidence that no such jurisdiction has been assumed.*

The agency has never established regulations nor invited actions for an adjudication in hearings before it of the "new" or "old" status of a drug.

So far as respondents are aware such proceedings have never been instituted during the thirty-four years the Act has been in force.

So far as respondents are aware the agency has relied entirely on the District Court for adjudicatory enforcement against new drugs unlawfully marketed without approved applications.

The agency obviously is confused as to whether it should or could proceed under Section 505 or under the Administrative Procedure Act. As yet it has never faced the issue in a practical context.

The rendering of advisory opinions is not an adjudicatory proceeding.

The agency by longstanding practice has acted upon the premise that a disputed issue as to the "new" status of a drug must be resolved in the District Court. It has never after thirty-four years administratively undertaken an adjudicatory hearing of this issue. See *Davis: Administrative Law Treatise*, ¶ 5.06, Vol. 1, pp. 324-220, 1958.

> "Against the Treasury's prior longstanding and consistent administrative interpretation its more recent ad hoc contention as to how the statute should be construed cannot stand." *United States v. Leslie Salt Co.*, 350 US 383, 396.

F. *Section 505 of the Act bestows no jurisdiction on the FDA to adjudicate whether a drug is "new".*

(1) *The preceding analysis shows that this issue is not material to any proceeding under Section 505.*

There is no basis in Section 505 from which jurisdiction of the Sercretary may be inferred to determine the applicability of Section 201 (p) to a product.

The information required in a new drug application, the criteria for approval and for the withdrawal of approval, and the absence of expressly provided rights of appeal, all demonstrate that the issue of whether Section 201 (p) is or is not applicable is not to be decided by the Secretary under the jurisdiction granted by Section 505.

Equally persuasive is the fact that the applicant may not be refused the right to make its application. This is a valuable right which protects the applicant from the vagaries of official advice.

F(2) *If a new drug application is filed, the agency then has jurisdiction of such application. This jurisdiction does not depend on whether the drug is "new". No "threshold question" is raised for determination by the submission of an application.*

The petitioners' brief refers to the applicability of Section 201 (p) to a drug as a "threshold question" to be decided by it prior to acting upon a new drug application or withdrawing approval of an application.

"Threshold question" is an attractive and seductive phrase; but the applicability of Section 201 (p) to a product is a threshold over which the agency is neither urged nor invited by the provisions of Section 505. For the agency so much as to consider the applicability of 201 (p) when applying the provisions of 505 would be in patent derogation of its duties exactly prescribed by the detailed criteria of that Section.

The agency has no authority to deny an application on the ground that it does not consider the drug to be "new".

The agency has no authority to grant approval of an application on the premise that the drug is old or grandfathered, but must pass on the information submitted by the applicant. The applicant may point to well known, published studies conducted by others as part of his evidence, but the agency's decision must be based on that evidence – not on whether the product is generally recognized by qualified experts as safe and effective.

The agency has no authority to withraw approval of an application on the ground that it is no longer necessary, nor to decline to withdraw approval when adverse new material is discovered on the ground the product is already generally recognized as safe and effective.

The jurisdiction of the agency is created by the application itself, by nothing more and by nothing less. The application of 201 (p) to the product is irrelevant to that jurisdiction.

F(3) *The question of whether a drug is "new" is no different in its treatment under the Act from that of whether a food or drug is adulterated, misbranded, or otherwise sold under the prohibitions of the Act.*

The applicability of the new drug definition to a product, and the issue of whether an approval application must exist before that product may be lawfully marketed, stands simply on the same footing as the other prohibitions of the Act.

The prohibitions of the Act against the sale of misbranded and adulterated drugs, which define at great length when such conditions are deemed to exist (Sections 501 and 502), are fully as important in the policing of the industry as is the prohibition against sale of an unapproved new drug.

The prohibition against the sale of a misbranded drug is the basis upon which an ineffective grandfathered drug may be removed from the market.

The agency has never contended that it could administratively adjudicate a case of misbranding or adulteration. Yet nothing in the Act indicates that the agency's action against the sale of unapproved new drugs should proceed in a manner any different from its enforcement of the other important provisions of the Act. That enforcement is uniformly provided for by prosecutional action in a District Court (Sec. 302, 303 and 304). Jurisdiction is placed not in the agency but in the Court.

F(4) *The factual issues in an enforcement proceeding against a "new" drug unlawfully sold are generally simpler than those involved in a misbranding proceeding.*

The issue presented to a Court for decision as to whether a drug is "new" as that term is defined by Section 201 (p) is not a decision of a scientific fact (see Section 1 of argument, *supra*).

The issues of misbranding and adulteration are issues of scientific fact. The issue of whether a drug is "new" is, by contrast, an opinion issue only.

The question of whether in a misbranding proceeding a grandfathered drug is or is not effective in fact is thus more technical and complex than a "new" drug issue under 201 (p).

The Act makes no distinction between the jurisdictions of the agency and of the court based upon any special or unique character inherent in the issue of whether a drug is "new".

G. *Since the Food and Drug Administration has no jurisdiction to determine whether a drug is "new" it has no adjudicatory power under the Administrative Procedure Act to make such determination.*

The Administrative Procedure Act is available only when an agency has been invested with jurisdiction to decide the question at issue.

The Food and Drug Administration has no right to require industry to submit to *binding* adjudication in a proceeding before it, without specific legislative authorization to do so.

Prosecutorial enforcement of the prohibitions of the Act is directed to the jurisdiction of the District Court. Adjudicatory determination of whether a drug is "new" and sold in defiance of the prohibition of Section 301 (d), is not placed in the agency, nor is such adjudicatory determination provided as to adulteration or misbranding (301, a, b, c).

CONCLUSION

In summary this brief has demonstrated that whether a drug is "new", as defined by Section 201 (p) of the Act, is not material to the Secretary's responsibilities in approving, disapproving or withdrawing approval of a new drug application under the provisions of Section 505 of the Act. The question of whether a drug is "new" or "old" is of no concern to the Secretary under Section 505.

The jurisdiction of the Secretary under Section 505 of the Act is invoked simply by the filing of an application There is no "threshold question" for him to determine, nor may he divest himself of jurisdiction on the ground that the drug involved is no longer "new".

The Secretary's right to proceed against a "new" drug sold without an approved new drug application is no different from his right to proceed against adulterated food or mislabled "old" drugs.

His right is prosecutorial, not adjudicatory, and must be exercised by him in a proceeding in a District Court. Adjudicatory jurisdiction is vested in the District Court alone.

Therefore the decision of the Court of appeals for the Fourth Circuit should be affirmed.

Respectfully submitted.

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In the Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-666

USV PHARMACEUTICAL CORPORATION, PETITIONER

v.

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

BRIEF FOR THE RESPONDENTS

OPINIONS BELOW

The opinion of the court of appeals (A. 466–473) is reported at 461 F. 2d 223. The opinion of the district court (A. 463–466) is not yet reported.[1]

JURISDICTION

The judgment of the court of appeals (A. 474) was entered on May 24, 1972. A petition for rehearing was denied on July 5, 1972. The Chief Justice extended the time within which to file a petition for a writ of certiorari until October 30, 1972. The petition was filed

[1] The district court's opinion appears at CCH Food, Drug, and Cosmetic L. Rep. ¶ 40,489.

on that date, and was granted on January 8, 1973. The jurisdiction of this Court rests on 28 U.S.C. 1254(1).

QUESTIONS PRESENTED

Whether Section 107(c)(4) of the Drug Amendments of 1962 exempts from the Amendments' drug effectiveness requirements—

1. Certain categories of ineffective drug products with respect to which a new drug application was on file with the Food and Drug Administration at the time the 1962 Amendments went into effect.

2. Ineffective drug products marketed prior to the 1962 Amendments without an application on file, but which are identical or substantially similar to products for which an application was effective.

STATUTES INVOLVED

Pertinent provisions of Sections 201(p) and 505 of the Federal Food, Drug, and Cosmetic Act of 1938, 52 Stat. 1040, are reproduced at A. 482–484. These provisions, as amended by the Drug Amendments of 1962, 76 Stat. 780, 788–789, are set forth at A. 475–481.

Section 107(c) of the Drug Amendments of 1962, 76 Stat. 788–789, note following 21 U.S.C. 321, provides:

> SEC. 107(c)(1) As used in this subsection, the term "enactment date" means the date of enactment of this Act; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.
>
> (2) An application filed pursuant to section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be

deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date by virtue of paragraph (2) of this subsection—

(A) the amendments made by this Act to section 201(p), and to subsections (b) and (d) of section 505, of the basic Act insofar as such amendments relate to the effectiveness of drugs, shall not, so long as approval of such application is not withdrawn or suspended pursuant to section 505(e) of that Act, apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application, but shall apply to any changed use, or conditions of use, prescribed, recommended, or suggested in its labeling, including such conditions of use as are the subject of an amendment or supplement to such application pending on, or filed after, the enactment date; and

(B) clause (3) of the first sentence of section 505(e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application (except with respect to such use, or conditions of use, as are the subject of an amendment or supplement to such approved application, which amendment or supplement has been approved after the enactment date under section 505 of the basic Act as amended by this Act) until

whichever of the following first occurs: (i) the expiration of the two-year period beginning with the enactment date; (ii) the effective date of an order under section 505(e) of the basic Act, other than clause (3) of the first sentence of such section 505(e), withdrawing or suspending the approval of such application.

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

STATEMENT

This is one of five interrelated cases pending before the Court on writs of certiorari involving the Drug Amendments of 1962, P.L. 87–781, 76 Stat. 780 *et seq.*, which amended the definition of "new drug" in Section 201(p) of the Federal Food, Drug, and Cosmetic Act of 1938, 52 Stat. 1040 *et seq.*, to include the concept of drug effectiveness, and which added a requirement for drug effectiveness to the provisions for administrative clearance and supervision of drugs contained in Section 505 of the Act.[2] A back-

[2] The other cases are: *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, No. 72–394; *Hynson, Westcott and Dunning, Inc.* v. *Weinberger*, No. 72–414 (cross-petition); *CIBA Corporation* v. *Weinberger*, No. 72–528; and *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72–555.

ground statement describing the general history and operation of the statutes involved is set forth at pp. 3–25 of the government's brief in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72–555 (the "*Bentex* case"). We respectfully refer the Court to that statement for purposes of this case as well.

Briefly, the 1938 Act provided in Section 505, 52 Stat. 1052 (A. 483) for a system of administrative pre-marketing clearance and subsequent administrative supervision of any "new drug." Such a drug was defined as any drug not generally recognized by qualified experts as safe for its intended use. Section 201(p)(1), 52 Stat. 1041, 1042. A new drug could not lawfully be marketed unless there was effective with respect to it a "new drug application" ("NDA") filed with the Food and Drug Administration to establish its safety for use. Section 505(a) (A. 483).

In the Drug Amendments of 1962, Congress modified these provisions by adding the further requirement that drugs be demonstrated to be effective, as well as safe, for their intended use. In Section 107(a), 76 Stat. 788, Congress provided that the 1962 Amendments should take effect on the date of enactment, October 10, 1962, except as otherwise provided. In Section 107(c), the Amendments set forth specific provisions governing the application of the new "effectiveness" standard to drugs already being marketed when the 1962 Amendments took effect. This case involves the interpretation of these transition provisions.

Petitioner sells a line of drugs containing citrus bioflavonoid as a principal active ingredient (A. 276).

Bioflavonoids are chemicals extracted from fruit skins (A. 371). When used in the dosage recommended for petitioner's products, they are not pharmacologically toxic in the sense that a normal individual would develop adverse reactions from them (A. 370–371).

All of petitioner's products contain the identical citrus bioflavonoid compound. New drug applications for petitioner's products became effective as follows (A. 368):

	Effective date
NDA 9965:	
CVP Capsules	Nov. 8, 1955
CVP Syrup	Nov. 8, 1955
CVP with Vitamin K Syrup	Nov. 8, 1955
(Supplement):	
CVP with Vitamin K Tablets	Jan. 19, 1956
Duo-CVP Capsules	
NDA 11474: Prednyl	[3] Aug. 26, 1956
NDA 11475: Prednis-CVP	Aug. 26, 1956

No NDA was ever filed with respect to "Duo-C.V.P. with Vitamin K Capsules" or "Bivam" (A. 368).

On April 19, 1961, the Director of the New Drug Branch of the Bureau of Medicine in the Food and Drug Administration advised petitioner that two of these products, Prednyl and Prednis-CVP, were not, "[i] our opinion * * * new drugs when distributed under the labeling provided for in the respective new drug applications" (A. 300, 369). That labeling recommended use of the drugs in the treatment of capillary fragility and permeability occurring in various conditions. The Director declined to comment on the status of other products because the final printed labeling for

[3] Prednyl was no longer marketed in the United States when the Drug Amendments of 1962 became effective (A. 368).

them was not on file with the agency (A. 300).[4] On May 16, 1961, petitioner submitted the labeling and stated that "[i]t is our recollection that the C.V.P. class of products were no longer considered to be new drugs a short time after the N.D.A. became effective" (App. 301). FDA did not respond to that letter.

Petitioner's C.V.P. products were described in its labeling as a water-soluble biologically active flavonoid compound made from citrus peel and pulp combined with ascorbic acid, which maintains the integrity of capillary walls and thus helps to increase capillary integrity and aids in preventing abnormal capillary permeability, fragility and bleeding. They were recommended to correct all ailments involving bleeding, including habitual and threatened abortion; postpartum bleeding; epistaxis, otolaryngology, tonsillectomy; purpura, ecchymosis; hypertension; "little strokes"; diabetic retinitis, ocular disorders; bleeding gums, gingivitis, pyorrhea, periodontal conditions; menorrhagia, RH incompatibility; certain respiratory conditions; rheumatoid arthritis; hermorrhagic duodenal ulcer and ulcerative colitis; hemorrhagic cystitis; postoperative bleeding; and radiation therapy (A. 306–318, 398).

After enactment of the 1962 Amendments, petitioner's products, together with a large number of other bioflavonoid products, were reexamined by the Food and Drug Administration under the drug effectiveness

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[4] Because of the 1962 Amendments, FDA, by regulation adopted May 28, 1968, revoked all opinions previously given that products were not new drugs. 33 Fed. Reg. 7758, 21 C.F.R. 130.39 (A. 291).

criteria contained in the new provisions of the law.[5] The initial review was undertaken by NAS-NRC panels under the drug efficacy study program (described in our brief in *Bentex* at pp. 16–19). In the words of the NAS-NRC Panel on Drugs Used in Metabolic Disorders, "everything from threatened abortions to bleeding gums is reported to have responded" to treatment with citrus bioflavonoids. This Panel's evaluation was that the "use of these materials as hemostatic agents for capillary fragility is felt to be unjustifiable and not proved." See App. A, *infra*, p. 56. The NAS-NRC Panel on Drugs Used In Hematologic Disorders found, in the words of one of its members, that there was no demonstration "in any form, in any combination, with respect to the bioflavenoids" that these products are efficacious for any medical use (A. 347).

These conclusions were based on a consideration of the material submitted by USV and others marketing bioflavonoid products, on information available in the published medical literature, and upon the informed judgment of the panel. The expert groups considered all the bioflavonoid preparations in terms of their claimed usefulness in bleeding disorders and found no evidence of efficacy for any bioflavonoid, including USV's, for any bleeding state in man (A. 344–345, 359–360). Reports of the panel findings were transmitted to the agency.

On January 23, 1968, the Food and Drug Administration announced that, after considering the NAS-NRC reports concerning bioflavonoid compounds, it

[5] FDA's implementation of the 1962 Amendments is described in the government's *Bentex* brief at pp. 16–23.

had concluded from the reports and its own evaluation that there was no evidence that these drugs are effective for use in man for any condition. 33 Fed. Reg. 818 (A. 290). The notice advised interested persons that the Commissioner of Food and Drugs intended to publish a notice of opportunity for hearing on a proposal to withdraw approvals for all "new-drug applications" for drugs containing these compounds, alone or in combination with other drugs. The announcement was made to notify interested persons and to invite all persons who might be adversely affected to meet and discuss problems arising from the agency's intentions (*ibid.*).

On July 10, 1968, FDA issued a formal notice of opportunity for hearing on its proposal to withdraw approvals of the NDAs on these products, including petitioner's nine products covered by NDAs 9965, 11474 and 11475.[6] 33 Fed. Reg. 9908 (A. 293–296). Petitioner then filed this suit in the district court, seeking a declaratory judgment that its drugs are exempted from compliance with the efficacy requirements of the 1962 Amendments by the provisions of Section 107(c)(4) (A. 275).

In the meantime, the administrative proceedings went forward. USV sought a postponement because of the pending litigation concerning its products' status, but the Commissioner declined to stay the proceedings. Petitioner submitted no evidence of adequate and well-controlled clinical investigations to support

[6] We are here utilizing the phrase "covered by" in the sense that we contend it is used in Section 107(c)(4) of the 1962 Amendments. Two of the nine products were not actually named in any of these NDAs (see p. 6, *supra*).

its claims of effectiveness, and the Commissioner, on October 15, 1970, concluded that there was a lack of substantial evidence that petitioner's products, for which NDAs had been in effect, were therapeutically effective as claimed in their labeling. Approvals for petitioner's NDAs were therefore withdrawn.[7] 35 Fed. Reg. 16332 (A. 297–298).

In the district court, petitioner contended that its products were exempted by Section 107(c)(4) because (1) they had been sold in the United States on the day prior to enactment of the Drug Amendments of 1962 (*i.e.*, October 9, 1962); (2) they were not new drugs under the 1938 Act because they were generally recognized as safe; and (3) they were, in petitioner's view, not "covered by an effective application." In support of its claim of general recognition of safety, petitioner offered the testimony of three physicians, Drs. Karpman (A. 422–434), Clemetson (A. 434–442)

[7] On petition for review, the Court of Appeals for the District of Columbia Circuit reversed the Commissioner's decision, because the Commissioner's notice of opportunity for hearing and final order failed to set forth the facts and reasons relied upon in denying petitioner the hearing it had requested and in withdrawing the NDA approvals. *USV Pharmaceutical Corporation* v. *Secretary of Health, Education and Welfare*, 466 F. 2d 455. Although the government believes the court of appeals was in error insofar as its opinion would impose on the Commissioner a burden of coming forward with evidence of inefficacy before refusing to hold an evidentiary hearing (an alternative ground of decision), it did not seek review of the decision in this Court. The proceedings on remand are now pending before the Commissioner, but action on USV's request for a hearing has been stayed pending a decision in *Weinberger* v. *Hynson, Westcott and Dunning, Inc.*, No. 72–394, since the operation of FDA's regulations governing availability of hearings are at issue in that case.

and Miller (A. 442–463). Petitioner also relied on the government's stipulation that its products would not cause toxic adverse reactions in normal individuals. To establish that its products were not "covered by" effective applications, it relied upon the 1961 statement of the Director of FDA's New Drug Branch that "[i]n our opinion" Prednis-CVP and Prednyl were not new drugs, on its assertion that CVP products were no longer considered to be new drugs a short time after the NDA became effective (A. 300–301), and on the statement of its counsel that petitioner had not complied with FDA regulations requiring the submission of information concerning new labeling and changes in the method of manufacture of new drugs (A. 451–452).

On April 1, 1971, the district court held that two of petitioner's products had never been covered by effective NDAs and that the other seven had been covered at one time, but that these applications had later been withdrawn by petitioner. It further found that the products were "safe" for use in treating capillary permeability and fragility.[8] It therefore concluded that, as of the day the 1962 Amendments

[8] The government had relied on the testimony of Dr. Spaet, who had served on the NAS–NRC hematology panel and had the primary responsibility for the evaluation of bioflavonoid drugs, and of Dr. Corn, another expert witness, to show that petitioner's products were not safe because they were not effective to treat any condition involving bleeding, whether resulting from capillary permeability or fragility or any other condition (A. 371–422). However, since the question was not presented in the petition for certiorari, it is not necessary on this record to determine whether, as a matter of law, a product could have been unsafe prior to the Drug Amendments of 1962 because it was ineffective in treating the conditions for which it was recommended in its labeling.

became effective, petitioner's products were not new drugs, were not covered by effective applications within the meaning of Section 107(c)(4), and hence were exempted from the effectiveness criterion added to the regulatory provisions of Sections 505 and 201(p) (A. 463–466). In so ruling, the district court necessarily determined that it, and not the Food and Drug Administration, had jurisdiction to decide exemption questions.

On appeal, the court of appeals, while agreeing that the district court alone had jurisdiction,[9] reversed on the merits and held that none of petitioner's bioflavonoid products were entitled to the Section 107(c)(4) exemption (A. 466–473). As to the seven drugs for which NDAs had been filed, the court stated that USV was without authority to withdraw an NDA once it was effective. Therefore, even if the drugs were generally recognized as safe on October 9, 1962, they nevertheless were "covered by an effective application" within the meaning of Section 107(c)(4) and thus were not exempt from the drug effectiveness requirements of the 1962 Amendments (A. 468–470). As to the two "me-too" drugs,[10] the court held that, although the me-toos of other manufacturers competing with USV's bioflavonoids would be exempt, USV's me-toos were not exempt because the NDAs covering its pioneer drugs, which were personal to USV, covered all of its products similar in

[9] This issue is discussed in the government's brief in the *Bentex* case.

[10] Use of the term "me-too," which describes identical, similar, and related drug products, is explained in the government's brief in the *Bentex* case at p. 7, and at 37 Fed. Reg. 23185, which added Section 130.40 to 21 C.F.R.

formula and labeling (A. 470–473). In response to USV's petition for certiorari, the government agreed that USV's me-too products should be accorded the same treatment as me-toos of other manufacturers who had never filed NDAs for any bioflavonoid product; the government and USV disagree, however, on what that treatment should be.

SUMMARY OF ARGUMENT

This case presents issues of the scope of the exemption afforded to some drugs on the market at the time of adoption of the 1962 Drug Amendments by the provisions of Section 107(c)(4).

The legislative history of the 1962 Amendments shows that the Senate originally reported a bill that, by excluding effectiveness from the definition of "new drug" in Section 201(p), would have made all drugs then on the market exempt from new drug regulation for effectiveness if they were not "new drugs" as of 1962 under the old, safety-only definition. However, that bill was not enacted. Instead, after the thalidomide tragedy came to light, substantial revisions were made to the bill, including the addition of transitional provisions in Sections 107(c)(2) and 107(c)(3) making the drug effectiveness provisions specifically applicable to drugs already on the market, with a limited exception in Section 107(c)(4) for drugs which had "never been subject to" new drug regulation.

The construction of Section 107(c)(4) basically adopted by the court of appeals and urged here by petitioner would exempt from the Amendments' efficacy requirements any individual drug product not

specifically named in an application filed with the agency before 1962, even though one or more pharmacologically identical products that differ only in having been specifically named in an NDA would be subject to removal from the market for failure to establish effectiveness. This discrimination between "me-too" and "pioneer" products, which are identical to one another for any relevant regulatory purpose, is irrational and would raise serious constitutional problems. It would also, because the quantity of me-too products on the market far outnumbers the NDA'd versions of most drugs, create a situation in which, contrary to the apparent congressional purpose and expectation, the coverage provisions of Section 107(c) would be overwhelmed by the exemption provision. Since the legislative history contains no evidence that Congress intended such results, this Court should reject petitioner's construction of Section 107(c)(4).

With respect to its NDA'd products, petitioner contends that the applications in which they were named were no longer "effective" within the meaning of Clause (C) of Section 107(c)(4) because petitioner had "withdrawn" or "inactivated" them. This argument was rejected by the court of appeals, which held that an application that had gone into effect at any time prior to 1962 remained an effective application for purposes of the exemption provision regardless of the manufacturer's subsequent actions with respect thereto. This aspect of the court of appeals' holding is directly supported by the explanation in the Amendments' legislative history that the exemption provision applies to drugs that had "never been subject to" new

drug regulation, a description that obviously does not fit petitioner's NDA'd products. Moreover, petitioner's proposed construction would be subject to the same irrationality objections as its interpretation of the application of Section 107(c)(4) to me-toos, since it would impose arbitrary discriminations among identical products depending on how the manufacturer had treated the NDA after an effective application was no longer required for the marketing of the product.

The arbitrary and debilitating results that would follow from petitioner's interpretation of Section 107(c)(4) are not required by the language or structure of the statute. They hinge upon an unsubstantiated assumption that the word "drug" as used in that provision refers to an individual drug product rather than, in a generic sense, to a class of identical or substantially similar products related to one another by chemical composition and therapeutic use. The logic of the statute, however, indicates that the word "drug" was used generically in Section 107(c)(4). Only under this approach does the statute have a coherent meaning, which both effectuates the legislative purposes underlying its enactment and avoids unwarranted discrimination among identical products on the basis of historical peculiarities of marketing wholly unrelated to the regulatory objectives of the efficacy provisions.

Under this generic approach, the existence of an effective NDA with respect to any member of the generic class means that the drug, generically, is "covered by an effective application," from which it follows, *a fortiori,* that any example of the drug is also "cov-

ered" and ineligible for the exemption by virtue of Clause (C) of Section 107(c)(4). Similarly, the generic approach prevents the operation of the statute from turning on idiosyncracies of an individual product's pre-1962 regulatory history, since the inquiry would always be directed to the characteristics of the drug's generic class.

The generic approach is, moreover, mandated by the structure of the statute. Section 107(c)(4) is by its terms addressed to the application of Section 201(p)'s amended definition of "new drug." Since Section 201(p) clearly deals with drugs generically, its amplification in Section 107(c)(4) should be read in the same sense. The fact that drugs are not dealt with generically under Section 505, which establishes procedures for the content and evaluation of new drug applications, is entirely consistent with a generic approach to Section 107(c)(4). Applications are perforce physical documents submitted by particular persons and describing singular products, and it is manifestly appropriate that the portion of the legislation establishing procedures for dealing with these concrete entities, as well as the administrative practices developed in connection therewith, should assume a personalized and particularized character. But the particularized approach of Section 505 is inappropriate for the broader regulatory objectives of Sections 201(p) and 107(c)(4).

The generic approach to Section 107(c)(4) gives that exemption provision a limited but reasonable meaning that is wholly consonant with the congressional purposes in establishing efficacy requirements

for drugs while allowing a limited exception therefrom. There were a significant number of drugs marketed between 1938 and 1962 (almost entirely in the over-the-counter category) that consisted solely of old, established ingredients that had long been generally recognized as safe, but which, because they consisted of a new combination of ingredients or because they advanced new claims, would not be entitled to "grandfather" status under the 1938 Act. Unless such drugs proposed increased dosages or involved new combinations of components about which some safety question might have arisen, they would "never have been subject to" new drug regulation and would fit precisely within the class identified by Congress in the committee reports and debates as being exempted by Section 107(c)(4) from the effectiveness requirements of the 1962 Amendments. Otherwise, those requirements became applicable to pre-1962 drugs after a two-year grace period under the other provisions of Section 107(c).

ARGUMENT

I

THE STRUCTURE AND LEGISLATIVE HISTORY OF THE 1962 DRUG EFFECTIVENESS AMENDMENTS AND OF THE TRANSITIONAL PROVISIONS OF SECTION 107(C) INDICATE THAT THE EXEMPTION PROVISION OF SECTION 107(C)(4) SHOULD BE NARROWLY CONSTRUED

1. The basic thrust of the 1962 Amendments is to require manufacturers of drugs to establish their effectiveness for claimed uses, as well as their safety, before the products can lawfully be marketed. To accomplish this, Section 201(p) of the Act was amended to

redefine a "new drug" (*i.e.*, a drug subject to premarketing clearance by FDA) as one not generally recognized by experts as both safe and effective for use under the conditions prescribed;[11] Sections 505(a), (c) and (d), which had previously provided that an NDA would automatically become effective unless an order was issued refusing to permit it to become effective, were amended to require affirmative approval by FDA; Section 505(d), which deals with the procedures for administrative action on NDAs, was amended to require disapproval of an application if there is "a lack of substantial evidence that the drug will have the effect it purports or is represented to have"; and Section 505(e) was amended to require that any previously granted approval of an application be withdrawn whenever it appears from new information or otherwise that there is a lack of substantial evidence of the drug's effectiveness.

In Section 107(c) of the 1962 Amendments, Congress dealt with the problem of the application of the new drug efficacy provisions to drugs already on the market at the time of enactment of the Amendments. Without this transitional provision, all such drugs—except those marketed prior to the enactment date of the basic Act (June 25, 1938) whose labeling had not been changed, which were exempted from "new drug"

[11] The definition of "new drug" in Section 201(p) also includes a requirement that the drug be used "to a material extent or for a material time" (A. 475). For purposes of conciseness of expression, this brief usually refers to "general recognition" in discussing the criteria for "new drug" status. Such reference should be deemed to include the "use" requirement also imposed by the statute.

status by Section 201(p)—would immediately have been in violation of the amended Act unless generally recognized as effective. Even the approximately 9,000 NDAs which had become effective would not have authorized continued marketing of the products to which they applied, because the applications had not been affirmatively approved by FDA under the new criteria.

Section 107(c) contains four subparagraphs. The first subparagraph defines the term "enactment date" as the date of the enactment of the Amendments (October 10, 1962) and the term "basic Act" as the Federal Food, Drug, and Cosmetic Act.

The second subparagraph, Section 107(c)(2), is addressed to particular new drug applications on individual products filed prior to the Amendments. It provides that applications which were "effective" on the day before the enactment date shall be deemed to be "approved" under the Amendments. This provision was necessary because, under the original Act, NDAs had not been administratively approved; rather, they became automatically effective after a fixed period unless the Secretary refused to permit them to become effective. The amendments to Section 505(a) and (c), however, imposed a requirement of formal approval. Section 104, P.L. 87–781, 76 Stat. 784. Section 107(c)(2) thus eliminated the necessity to review and approve every application already on file.

The third subparagraph, Section 107(c)(3), is also concerned with particular applications previously on file. It provides that the amended provisions for the filing of an NDA in Section 505(b) and for approvals

or refusals to approve under Section 505(d), insofar as they relate to the effectiveness of drugs, shall not apply to applications already in effect, so long as the application is not withdrawn or suspended under Section 505(e), if the labeling remains unchanged. It further provides that in any proceedings to suspend or withdraw such an application, the new effectiveness requirement in the withdrawal provision, Section 505(e), shall not apply until October 10, 1964, or until the application is withdrawn for reasons other than lack of drug effectiveness, whichever comes first. Manufacturers were thus assured that they could continue marketing previously NDA'd products unless and until the NDA was withdrawn, and that before such a withdrawal could occur on the new efficacy grounds, they would be afforded a minimum of two years within which to compile "substantial evidence" in the form of adequate and well-controlled studies (see Section 505(d)) to support the claims for their products.

Finally, in Section 107(c)(4), Congress exempted certain drugs from the new effectiveness requirements, so long as their composition and labeling remained unchanged. In order to benefit from this exemption, a product would have to satisfy three requirements: (A) it must have been commercially used or sold in the United States on October 9, 1962; (B) it must not have been a new drug as defined in the pre-amendment Act (*i.e.*, it must have been generally recognized by experts as safe); and (C) it must not have been "covered by an effective application under section 505 of that Act" (A. 482).

The two issues presented in this case turn upon the proper interpretation of Section 107(c)(4): whether "me-too" copies of an NDA'd drug product are subject to the efficacy requirements to the same extent as the NDA'd product itself depends on the interpretation of the phrase "drug * * * covered by;" whether the NDA'd product may itself be exempted in certain circumstances depends on the interpretation of the word "effective." With respect to the first question, the court of appeals held that only the products named in the NDA (or me-toos of the same manufacturer) are "covered," and therefore identical or similar copies marketed by other manufacturers would be eligible for the exemption; we contend, on the other hand, that the phrase "drug * * * covered by" should be given a broader, generic meaning, so that me-toos would be subject to the same regulation for effectiveness as the NDA'd products they duplicate. With respect to the second question, the court of appeals agreed with the government's view that an NDA that became effective prior to 1962 remained effective for purposes of Section 107(c)(4) regardless of the subsequent history of the product, so that all products NDA'd between 1938 and 1962 are therefore ineligible for the exemption; petitioner urges that an NDA could cease to be effective, and the product therefore exempt, if the manufacturer had taken steps to inactivate or withdraw the NDA.

2. One of the major defects in the 1938 Act upon which Senator Kefauver's investigations of administered prices in the drug industry [12] focused was its

[12] See our brief in *Bentex* at pp. 10–11.

failure to prevent the marketing of drugs as to which there was no scientifically reliable evidence that they would be effective for the uses for which they were promoted. Testifying in 1961 in support of S. 1552, the bill that ultimately was adopted as the 1962 Amendments, then Secretary of Health, Education, and Welfare Ribicoff provided examples of drugs that FDA had been forced to approve for marketing despite the absence of any appropriate medical evidence that the drugs would actually do what was claimed for them (citrus bioflavonoids, the drugs involved in the present case, were among those singled out by Secretary Ribicoff as coming within this category).[13]

On July 19, 1962, the Senate Committee on the Judiciary reported a bill designed to "keep unfit drugs off the market * * * and speed their removal should they reach the market." S. Rep. No. 1744, Part 1, 87th Cong., 2d Sess., p. 8 (hereinafter referred to as "Senate Report"). The Committee recommended amendments to Section 505 of the Food, Drug, and Cosmetic Act, the provision governing the processing of NDAs, under which approval and withdrawal of approval would turn on evidence of efficacy as well as of safety. However, the reported bill did not propose any amendment of the definition of "new drug" in Section 201(p), so that any drug that was generally recognized as safe by qualified experts would not be subject to the Act, and thus not subject to its new efficacy requirements (*id.* at 17). Had the

[13] See Hearings before the Subcommittee on Antitrust and Monopoly of the Committee on the Judiciary, United States Senate, 87th Cong., 1st Sess., pursuant to S. Res. 52 on S. 1552, Part 5, pp. 2583–2585.

bill been enacted in this form, the result would have been that drugs then on the market would have been exempted from the efficacy requirement unless they were not then generally recognized as safe—in other words, as applied to drugs already on the market, the bill as initially reported would have had the same effect as the bill actually enacted would have if Clause (C) of Section 107(c)(4) were eliminated.

Senator Kefauver dissented from this aspect of the report, contending that if the definition of "new drug" were not amended to include effectiveness, new claims for, or variants of, products previously cleared under Section 505 would not be subject to efficacy review (*id.* at 36–37). The Committee majority rejected this view, pointing out (correctly) that such new uses already required clearance for safety under the 1938 Act, and therefore they would require clearance for effectiveness under the proposed amendments (*id.* at 17; see also statement of Senators Dirksen and Hruska, *id.* at 60–61). Had the bill been enacted in this form, petitioner's contention (Br. 52–60) that Congress did not seek to apply the efficacy provisions to safe drugs then on the market would have considerable force. But it was not.

Instead, at about the time the Committee reported out the initial version of the bill, the Nation (and the Congress) was jolted by news of the thalidomide tragedy. On August 3, 1962, President Kennedy submitted to the chairman of the Senate committee drafts of further amendments for the Committee's consideration which, the President stated in his letter of transmittal, "* * * will help assure the American people

that any drug on the market today is safe and effective for its intended use * * *." *Public Papers of President John F. Kennedy* 603 (1962). The committee thereupon met in executive session on six occasions between August 6 and August 20, and, on August 21, reported out a bill amended in a number of respects from the July version. Senate Report, Part 2, p. 1.

One of the amendments added general recognition of effectiveness to the "new drug" definition in Section 201(p). This change was stated to be for the purpose of eliminating "any possible ambiguity" regarding the problem that had disturbed Senator Kefauver (*id.* at 5). Petitioner contends that this limited expression of purpose shows that Congress did not intend by this change to subject drugs already on the market to the new effectiveness criteria (Br. 55). There is no reason, however, to resolve that contention in isolation, since Congress made clear its general intention that the new requirements would apply to such drugs by its adoption of the transitional provisions in Section 107(c). Subparagraphs 2 and 3 of that Section (as explained at pp. 19–20, *supra*) established the basic proposition that drugs then on the market with effective NDAs would be considered to have approved NDAs and could continue to be marketed but would, after a two-year grace period, be subject to removal from the market through NDA withdrawal proceedings on inefficacy grounds. Section 107(c)(4) created an exception from this general policy only for drugs then on the market that were generally recognized by experts as safe *and* were not "covered by an effective application."

That this exception from the general principle was intended to be a limited one was made clear by the report (Senate Report, Part 2, p. 8; emphasis supplied):

> Thirdly, in the case of a drug on the market which was *never subject to the new-drug procedure before,* the amendments to the new-drug definition relating to drug effectiveness would not apply to existing labeling claims.

Senator Eastland explained the transitional provisions in a similar manner on the Senate floor (108 Cong. Rec. 17366; emphasis supplied):

> As a result of the change in the definition of "new drug" and the addition of the new effectiveness test, it is necessary to include transitional provisions. Under these provisions, the new effectiveness test, in the case of drugs previously cleared under a new drug application, will apply only to new or amended claims *unless [approval of] the application is withdrawn or suspended.* Withdrawal on the ground of a lack of substantial evidence of effectiveness will not apply, for a period of 2 years, to existing claims, unless the approval of any of the claims is withdrawn on other grounds. Established drugs *which have never been required to go through new drug procedures* will not be affected by the new effectiveness test insofar as their existing claims are concerned.

Petitioner's argument that the post-thalidomide revisions to the legislation had "a clear, narrow and limited [purpose]—to insure that 'an NDA'd drug would not make new, unsupported claims of efficacy' " (Br. 59–60) is thus erroneous. The bill would have

achieved this purpose under both the original and the amended version, and, as Senator Eastland made unmistakably clear, the added "transitional provisions"—and it is significant that he used that term—had the further effect of permitting FDA to withdraw or suspend an NDA for inefficacy with respect to *existing* claims after the two-year grace period.

Substantially the same explanation appears in the House Report (H. Rep. No. 2464, 87th Cong., 2d Sess., pp. 8, 12) and the Conference Report (H. Rep. No. 2526, 87th Cong., 2d Sess., pp. 22–23) both of which similarly refer to Section 107(c) as adding "transitional provisions." The history of the amendments in the House sheds little new light on the congressional intent and affords no concrete support for petitioner's contention (Br. 58–59) that Section 107(c)(4) was a compromise designed to exempt me-toos from efficacy regulation. If anything, it tends to confirm that the basic thrust of the legislation was to cover pre-1962 drugs, with a limited exemption carved out for drugs that, as a generic class, had always been recognized as safe from the time they first went on the market.[14] (See discussion at pp. 42–52, *infra*.)

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[14] In May 1962, Representative Harris, Chairman of the House Committee on Interstate and Foreign Commerce, introduced H.R. 11582, 87th Cong., 2d Sess., to give effect to a part of President Kennedy's message on consumer protection. This bill provided for the inclusion of efficacy in the definition of "new drug" and in the administrative provisions in Section 505. It also contained, in Section 108(c), transitional provisions similar in effect to Section 107(c)(3) of the final Act, which would have had the effect of subjecting all pre-1962 drugs to the efficacy requirements. Hearings were held on the House bill before and after the Senate had passed S. 1552 in August 1962. *Drug Industry Act of 1962*, Hearings before the House Com-

In summary, beyond repeated statements to the effect that Section 107(c)(4)'s exemption applies to drugs that were "never subject" to new-drug regulation and was part of "transitional provisions" for applying the efficacy requirements to "existing" drug claims, Congress provided little elucidation of the scope and application of the exemption. However, there are indications that the distinction that Congress had in mind was between "ethical" or prescription drugs, and so-called "proprietary" or "over-the-counter" drugs. Prescription drugs, which by definition involve products that may be dangerous unless

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mittee on Interstate and Foreign Commerce, 87th Cong., 2d Sess. on H.R. 11581 and 11582 (June, August 1962). At these hearings, one witness for the Pharmaceutical Manufacturers Association urged the position initially adopted (but subsequently rejected) by the Senate Committee, *i.e.*, that old drugs already on the market should not be subject to the effectiveness requirement, and that the NDA for new drugs cleared before the amendment should be withdrawn or suspended only if the product were unsafe. *Id.* at 238. The witness for the Proprietary Association, noting that most proprietary medicines had not been subject to new drug procedures, suggested that the revised definition of new drug should not apply to any drug intended for use under conditions set forth in its labeling on the date the amendments were enacted. *Id.* at 369. Responding to these suggestions, the FDA asked why ineffective drugs should be promoted because the manufacturer started selling "before a serious flaw in the act was corrected? On the other hand, we do not propose that these thousands of drugs be summarily taken off the drugstore shelves. We, of course, would suggest a reasonable transition provision." *Id.* at 573. As reported, the House bill included in Section 107 the provisions originally proposed, plus a new paragraph (d) closely parallel to present Section 107(c)(4). Nothing in this history suggests an intent to create an exemption that, in operation, would exclude the vast majority of pre-1962 drug products from the efficacy requirements.

administered under medical supervision,[15] would not be exempted because they almost invariably had been subject to the new drug regulatory procedures. Proprietary drugs, which were considered safe enough to be self-administered, consisted in many instances of relatively innocuous substances and therefore may never have been subject to "new drug" regulation. This is borne out by the testimony of a representative of the Proprietary ~~Drug~~ Association in the House hearings, see n. 14, *supra*. It is also supported by Senator Kefauver's explanation during the debates of differences in the bill's application to these two classes of drugs (108 Cong. Rec. 17368):

> Effectiveness, as well as safety, should apply to new proprietary drugs, but proprietaries now on the market are not to be subject under the present bill to the provisions requiring them, upon notice by the FOA [sic], to support their claims for effectiveness. I think they should be so required. That is a matter which can be remedied in conference or by other legislation.[16]

Even more significant than what the legislative history affirmatively reveals about congressional intentions, for purposes of the statutory interpretation

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[15] Under Section 503(b) of the Act, 21 U.S.C. 353(b), prescription drugs are products which may be habit forming, which for safety reasons should be administered only under supervision of a physician, or which are designated in the NDA as requiring distribution only by prescription. Such drugs, if marketed without prescription, are deemed misbranded.

[16] While this statement is generally accurate, there were in fact several hundred NDAs that became effective prior to 1962 for "proprietary" products. Those products, and their me-too copies, would of course be subject to the same regulation under Section 107(c) as similarly situated prescription drugs.

issues presented in the instant case, is what is absent. Petitioner has failed to cite, and we have been unable to find, a single reference indicating that Congress was aware of the regulatory status of me-too drug products—that for every product named in an NDA there were numerous identical or similar products on the market for which no NDA had ever been filed—and considered this situation in formulating the transitional provisions. On the contrary, it is apparent that when the word "drug" was used in the reports and debates, with respect to Section 107(c)(4), it was used in the generic sense to refer to a chemical compound or class of compounds rather than to refer to a particular brand or product.

II

THE EXEMPTION IN SECTION 107(c)(4) SHOULD BE CONSTRUED TO EXCLUDE FROM THE AMENDMENTS' EFFICACY REQUIREMENTS ONLY THOSE DRUGS WHICH, AS A GENERIC CLASS, WERE NEVER SUBJECT TO NEW DRUG REGULATION PRIOR TO 1962

Petitioner contends that it is exempted by Section 107(c)(4) from being required to establish the effectiveness of nine citrus bioflavonoid products that it has been marketing since before 1962. Seven of these products were named in three NDAs that became effective prior to 1962, while the other two were "me-toos" that were never the subject of an NDA. The two categories of products present different, although related, issues, the resolution of which depends upon the interpretation of three phrases in the provision, each of which is here italicized:

> In the case of *any drug* which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not *covered by* an *effective application* under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day. [Section 107(c)(4); emphasis added.]

The interpretation of the phrase "any drug" is important to the resolution of both issues presented by this case. It is our view that the phrase should be read in a generic sense, *i.e.*, as referring to pharmacologically identical or substantially similar classes of items defined by chemical composition and therapeutic use.[17] Under this interpretation, all drug products belonging to the same generic grouping would be treated the same for purposes of Section 107(c)(4) regardless of the particular history of any individual product. Petitioner, on the other hand, urges an approach under which the phrase would refer to individual drug products and the application of the provision to each individual product would turn on its peculiar regulatory history.

The interpretation of the phrase "covered by" is involved in the resolution of the me-too issue. Under petitioner's view, a particular drug product is "covered by" an application only if it was itself the subject of the application. Under the government's in-

[17] As used in this brief, "generic" always has this meaning.

terpretation, such a product is "covered by" an application if it is a member of a generic class, any one of which had been the subject of an NDA.

Finally, the interpretation of the phrase "effective application" is critical to the issue of FDA's power to withdraw approval of petitioner's NDAs for failure to establish efficacy. In the government's view, concurred in by the court of appeals, an application once filed remains "effective" for purposes of this provision regardless of the manufacturer's subsequent actions or of subsequent general recognition of the drug's safety. Petitioner urges that actions taken by the manufacturer to withdraw or inactivate the application would cause it to cease to be "effective" within the meaning of the provision.

A. PETITIONER'S INTERPRETATION OF SECTION 107(C)(4) AS APPLIED TO ME-TOO DRUG PRODUCTS WOULD DEFEAT THE BASIC PURPOSE OF THE STATUTE AND WOULD CAUSE ARBITRARY AND UNWARRANTED DISCRIMINATION AMONG MANUFACTURERS OF IDENTICAL PRODUCTS

Are me-too drug products "covered by" applications filed with FDA on identical drug products (either by other manufacturers or for other brands of the same manufacturer [18])? The phrase "covered by" is not defined in the Act and has no obvious inherent meaning. As a matter of pure language, considered

[18] The court of appeals distinguished between these two situations, holding that me-toos would be exempt from efficacy regulation in the former situation but not the latter. We agree with petitioner that the distinction is unwarranted. Our position is that all generically related drug products should be treated the same; but even if they are not, at least all me-toos should be accorded the same treatment.

in isolation, the government's interpretation and petitioner's are equally plausible. As a matter of implementing the statutory objectives and the apparent congressional intent, however, it would make no sense for Section 107(c)(4) to be applied in the manner petitioner suggests.

Petitioner's approach, which turns on the vagaries of the marketing and regulatory history of each individual product, introduces a fortuitous and wholly irrational element into the statutory scheme. Manufacturers who submitted to the congressionally established regulatory procedures and obtained an effective NDA for their products (sometimes hereinafter referred to as "pioneers") would be required to show effectiveness in order to continue marketing them. But their competitors, who produce the same drug for the same uses, would be exempt so long as they never obtained an effective NDA, even if their initial marketing had been illegal or had been made possible only because of the pioneer's NDA. In short, the producer of a drug who obtained the primary NDA would have to show effectivness, while the me-too manufacturer who copied it would not.

The basic purpose of the 1962 Amendments, insofar as here relevant, was to assure the American public that the drugs they use are effective as well as safe.[19]

[19] As Congressman Ryan put it (108 Cong. Rec. 21069):

"Once a company is registered and deemed qualified to produce drugs, the Food and Drug Administration must be given substantial evidence that each drug produced is effective as well as safe. Under present law a company could stick a name on bottled water and attempt to sell it for medicinal use simply because it is not harmful. This has been one of the greatest defects in our existing law; a producer should be required to

As we have indicated in our brief in *Bentex* (pp. 7–8), for every drug product for which an NDA was filed prior to 1962 there were generally a large number of me-too copies that went on the market without their own NDA (current experience indicates a ratio of about 13 to 1). If the interpretation of petitioner and the court of appeals is correct, Section 107(c)(4) would exempt all the me-toos from the efficacy requirements, leaving the Amendments effective only against the pioneers (in addition to post-1962 products). The exemption in Section 107(c)(4) would thus be broadened to the point of almost completely swallowing up the basic legislative action in

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show that his product will do what is claimed of it. When a person pays his money at the drug counter, he should have some degree of assurance of the efficacy of the product he buys."

Congressman Reuss echoed the same thought in explaining the purposes of the proposed drug effectiveness provisions (*id.* at 21070):

"So, as the thalidomide tragedy has shown, the Food and Drug Administration does now have limited authority that can prevent a major disaster resulting from the wide use of an unproven, insidious drug. But, the limited authority FDA now has is not enough to assure the high standards of quality, the reliability, and the effectiveness that our citizens have a right to expect in the drugs they take.

"All of the provisions in H.R. 11581 are important and necessary for the public good, but if I should point to one as being most important, it would be the provision that new drugs be proved effective before they are marketed.

"A dismal proportion of consumers' resources are spent on worthless drug products. This unnecessary and wasteful extravagance might not be so bad if it were not coupled with the deplorable fact that ineffective drugs can mean the difference between a man's health and sickness or his life and death. The bill before us would help to assure our sick that the drugs they take will in fact be effective in their purpose."

Sections 107(c)(2) and 107(c)(3) authorizing FDA to withdraw marketing appoval for pre-1962 drugs of unproved effectiveness, leaving those provisions an empty and meaningless shell (whose only effect, in most instances, would be to restrict competition in the marketing of ineffective pre-1962 drugs [20]).

Such a self-defeating purpose should not be assigned to Congess. Nor should Congress be presumed to have acted with the irrationality inherent in petitioner's construction of Section 107(c)(4). What conceivable purpose could Congress have had in exposing the NDA'd product to removal from the market for failure to establish efficacy while exempting its non-NDA'd twin? Surely if Congress wished to protect the public health and purse by removing the pioneer, it could hardly have intended to insulate the equally ineffective me-too. Conversely, if Congress wanted to protect the me-too from removal even though ineffective, in order to avoid adverse economic impact on the manufacturer as a result of the new requirement (the legislative history, discussed at pp. 21–29, *supra,* shows that it did not), there is no reason why it would have wished to deny the same benefit to the pioneer. A rational basis might be supposed for a discrimination in favor of the manufacturer who had shouldered the burden of submitting to the regulatory procedures under the Act, but none can be supplied for a discrimination against him.

Indeed, the arbitrary discrimination that would be imposed on some manufacturers to the benefit of

[20] The legislative history indicates that Congress was concerned with fostering rather than restricting competition. Senate Report, Part 1, p. 18.

competitors marketing identical products under petitioner's construction of Section 107(c)(4), apart from entailing manifest deviation from congressional intent, would appear to raise serious constitutional problems. See, *e.g.*, *Morey* v. *Doud*, 354 U.S. 457; *Hartford Co.* v. *Harrison*, 301 U.S. 459; *Mayflower Farms* v. *Ten Eyck*, 297 U.S. 266. See also *Graham* v. *John Deere Co.*, 383 U.S. 1, 5 (pointing out that the Constitution's patent clause imposes limitations on the power of Congress to grant monopolies). In these circumstances, it is a "cardinal principle" of statutory construction that this Court should adopt a construction of the statute by which constitutional problems will be avoided. *Crowell* v. *Benson*, 285 U.S. 22, 62.

The anomalies inherent in petitioner's construction are not vitiated, we submit, by what petitioner characterizes as the "bifurcated nature of the regulatory scheme" (Br. 63–65). It is true that the agency has power to initiate judicial action against ineffective drug products, new or old, under the misbranding provisions of the Act. This remedy is, however, almost completely ineffectual in dealing with the problems created by ineffective pre-1962 me-toos. Since there were, in FDA's estimation, tens of thousands of me-too prescription drug products on the market on October 9, 1962, for which NDAs were not in effect, all of which would remain on the market pending case-by-case removal for misbranding, decades of case-by-case litigation would be required before the congressional goal of removing drugs of unproven effectiveness

from the market could be achieved.[21] As a practical matter, therefore, the theoretical availability of other remedies against ineffective me-toos does not eliminate the unjustifiable discrimination against the pioneer inherent in petitioner's construction.[22]

Moreover, remitting the agency to case-by-case judicial proceedings as the sole remedy for removal of ineffective me-toos from the market would be contrary to the basic scheme of the Act, which, as we have shown in our brief in *Bentex* (pp. 40–47), contemplates that administrative control through pre-

[21] Litigation of a small number of misbranding cases against over-the-counter drug products, with each case taking months or even years to resolve, has consumed an enormous amount of the agency's medical, compliance, and legal personnel resources without making a perceptible dent in the marketing of ineffective over-the-counter drugs. A classic illustration is the agency's attempt over more than a decade to remove from the market phenylpropanolamine drugs promoted for weight reduction. After a number of successful court actions against specific examples of the drug (*e.g.*, *United States* v. *60 28-Capsule Bottles, More Or Less, Etc.*, 211 F. Supp. 207, 214 (D. N.J.), affirmed *per curiam*, 325 F. 2d 513 (C.A. 3), these drugs are still on the market. Hearings on Advertising of Proprietary Medicines before the Subcommittee on Monopoly of the Senate Select Committee on Small Business, 92d Cong., 2d Sess., pp. 1239–1241. The agency has accordingly abandoned the case-by-case approach to over-the-counter drugs in favor of a broad rulemaking approach. See 37 Fed. Reg. 85, 9464.

[22] This is further emphasized by the difference in burden of proof on the issue of effectiveness in administrative proceedings implementing the Amendments and in judicial proceedings enforcing misbranding provisions—in the former, the manufacturer bears the burden of presenting substantial evidence of the product's effectiveness; in the latter, ineffectiveness must be proved by the government. See *Ubiotica Corp.* v. *Food and Drug Administration*, 427 F.2d 376, 378 (C.A. 6); *United States* v. *60 28-Capsule Bottles, More or Less, Etc*, *supra*.

marketing clearance and subsequent supervision by the expert administrative agency will be the primary safeguard of the public interest. One of the basic purposes of the 1938 Act was to remedy the inadequacies of the Food and Drug Act of 1906, which provided only judicial sanctions against misbranded or adulterated products. The 1962 Amendments were intended to strengthen the system of administrative clearance established under the 1938 Act by extending it to drug effectiveness claims. Indeed, the House Committee Report on the amended bill specifically indicates that it was designed to remedy the inadequacy of restricting the agency's powers with respect to ineffectiveness to case-by-case litigation for misbranding, as a result of which "good medical practice is hampered, and the consumer is misled until, perhaps years later, the Government has gathered the necessary evidence to sustain its burden of proving the violation in court." [23] Petitioner's contention would make this elaborate legislative effort an empty gesture by excluding power to proceed administratively with respect to the thousands of me-too products, thereby rendering virtually pointless the limited regulatory authority petitioner would concede to the agency with respect to NDA'd products.

This Court has often held that statutes should not be so construed that they produce unfair results inconsistent with their spirit and purpose. Rather, where a statute is drafted in a way which is susceptible of more than one interpretation, the courts should select the construction that will best achieve

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[23] H. Rep. No. 2464, *supra*, at 3.

the legislative objective.[24] This principle is particularly important with respect to claims for exemption from statutes intended to protect the public health. *United States* v. *Bacto-Unidisk*, 394 U.S. 784, 798; *United States* v. *Sullivan*, 332 U.S. 689; *United States* v. *Dotterweich*, 320 U.S. 277, 283–284. If Section 107(c)(4) is read, as we contend it should be, to apply to drugs as generic classes, rather than as individual products, it harmonizes with the legislative purpose declared for it, becomes internally consistent, and dovetails neatly into the definition of new drug in Section 201(p), which it modifies.

B. PETITIONER'S INTERPRETATION OF SECTION 107(C)(4) AS APPLIED TO NDA'D PRODUCTS IS ALSO UNREASONABLE AND CONTRARY TO THE EXPRESSED CONGRESSIONAL INTENT

The instant case and the cross-petition in *Hynson* (No. 72–414) both raise issues involving the eligibility for Section 107(c)(4)'s exemption of products that were the subject of an NDA filed between 1938 and 1962, but had, by October 9, 1962, come to be generally recognized as safe.[25] Hynson contends that general rec-

[24] See, *e.g.*, *United States* v. *American Trucking Assn's.*, 310 U.S. 534, 542–545; *Boys Market* v. *Clerks Union*, 398 U.S. 235, 250; *Puerto Rico* v. *Shell Co.*, 302 U.S. 253, 258.

[25] The fact that a drug is not toxic does not necessarily establish that it was generally recognized as safe by qualified experts within the meaning of Section 201(p) of the 1938 Act. Safety is a relative concept. Some drugs which are highly dangerous may be generally accepted as safe for use in treating extremely serious or life-threatening conditions, because the condition itself is more hazardous to the patient than the dangers of the drug. Conversely, ineffective but non-toxic drugs may be considered unsafe for use in treatment of serious conditions, if their

ognition of safety by that date, by removing the product from new drug status and regulation, is sufficient to meet the requirements for exemption from efficacy regulation. We answer that contention in our brief in No. 72–414.

Petitioner in the instant case concedes *arguendo* that mere termination of "new drug" status in that sense was not sufficient to satisfy the requirements of Section 107(c)(4). It contends, however, that in this case other steps were taken by the manufacturer and acquiesced in by FDA that had the effect of withdrawing the NDAs prior to October 9, 1962. In such circumstances, petitioner argues, the NDA should not be considered "effective" for purposes of Clause (C) of Section 107(c)(4). The court of appeals held, however, that petitioner had no power to "withdraw" the applications, and that petitioner's NDA'd products were therefore "covered by an effective application" and ineligible for the exemption from efficiency regulation. We agree.

The simplest answer to petitioner's contention is that it is directly contrary to the congressional explanation of the effect of Section 107(c)(4), reiterated in the Senate report (Part 2, p. 8), the House report (H. Rep. No. 2464, *supra,* at 12), the Conference report (H. Rep. 2526, *supra,* at 22–23), and Senator Eastland's explanation of the bill (108 Cong. Rec. 17366). Each of these sources specifically explains that the provision would exempt drugs that had *never* been

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use displaces effective therapy and thereby jeopardizes the patient's health or life (A. 334–335). The expert judgment involved turns on a balancing of risks.

subject to new drug regulation. See pp. 25–26, *supra*. No other category of drugs was said to be qualified for the exemption. Whatever steps petitioner may have taken to withdraw or inactivate its NDAs,[26] and whatever arguments it may advance on behalf of its me-too products, it obviously cannot, with respect to its NDA'd products, satisfy the congressionally intended requirement that in order to enjoy exempt status a drug must "never" have been subject to new drug regulation.

Even had Congress not clearly stated its intention that a drug that was subject to new drug regulation

[26] We do not agree that petitioner "effectively withdrew" its applications on bioflavonoid products. Its carefully phrased correspondence with the agency prior to the Amendments (A. 299–301) did not state that any application was being withdrawn. Rather, it simply stated that "[i]t is our recollection that the C.V.P. class of products were no longer considered to be new drugs a short time after the N.D.A. became effective" (A. 301). FDA's failure to challenge either petitioner's assertion or petitioner's failure to comply with reporting requirements for new drugs did not mean that the applications were withdrawn for purposes of Section 107(c)(4). The mere failure of an agency with limited resources to prosecute a violation does not, except for the statute of limitations, exempt the violator from the law's requirements. Moreover, as the court of appeals rightly observed, nothing in the 1938 Act authorizes a manufacturer to withdraw an NDA, either directly or indirectly, once it has become effective. Indeed, prior to the 1962 Amendments FDA itself had no authority to withdraw an NDA; it could only suspend the effectiveness of an application under specific substantive and procedural standards. See Section 505(e), 52 Stat. 1053. In view of the specificity with which Congress delimited the powers of the agency and the absence, prior to 1962, of any reason for the FDA to enforce reporting requirements against noncomplying holders of inactive NDAs, petitioner's purported withdrawal had no effect on its products' status under Section 107(c)(4).

at any time prior to 1962 would be subject to the Amendments' efficacy requirements, petitioner's proposed construction would be contrary to the principle that statutory provisions should be construed in a rational manner. Congress could rationally have decided that all drugs on the market in 1962 and generally recognized as safe at that time would be exempted from efficacy regulation simply by showing that they were so marketed and recognized—that is, indeed, what S. 1552 as originally reported in July 1962 would have done (see pp. 22–23, *supra*). But having rejected that approach, Congress had no basis in either policy or fairness to differentiate between products merely according to whether their manufacturer had taken steps to withdraw or inactivate the NDA.

To illustrate, there were 43 applications on file with FDA covering bioflavonoids and related compounds (A. 294–296). Most or all of these were in the same posture in 1962 as regards general recognition of safety, and all are considered of equally unproven effectiveness for their claimed uses by FDA. While the state of activity, inactivity, or withdrawal of these applications varied from one to the next, this provides no rational basis for discriminating among them for the purposes of the Amendment's efficacy requirements. Thus, petitioner's interpretation of this aspect of Section 107(c)(4) is subject to the same irrationality objection as its concept of me-too coverage.[27]

[27] Moreover, if the government's generic interpretation of the provision is accepted with regard to the me-too issue, the alleged "withdrawal" of petitioner's NDAs would be without

Under the generic interpretation, this irrationality is eliminated, since all products in a class of identical or substantially similar drugs are treated in the same manner. If the drug itself was subject to "new drug" regulation for safety prior to 1962, all examples of it are now subject to "new drug" regulation for effectiveness. If it was never subject to safety regulation, generically, none are, in the absence of changed composition or labeling.

C. A GENERIC APPROACH TO SECTION 107(C)(4) FULLY ACCORDS WITH THE STRUCTURE AND PURPOSES OF THE ACT

It is our contention that the word "drug" in Section 107(c)(4) must be accorded a generic meaning if the provision is to have a rational construction consonant with the overall language, structure, and purposes of the statute. Such an approach simply and sensibly resolves all the problems of interpretation presented by the provision. It does so by directing attention to the conformity of the generic drug with the three requirements set forth in the provision and assuring that all members of the class, which are, after all, the same for practical regulatory purposes, are accorded the same treatment. We further submit, contrary to the arguments of petitioner and the conclusion of the court of appeals, that such an approach is entirely consonant with the administrative history of the Act and the recognized personal character of an NDA under Section 505, and that it ascribes a sensible meaning to the exemption provision which conforms to the apparent congressional intent.

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significance, since its products would still be "covered by" the other NDAs on file for similar products, most of which had not been "withdrawn."

1. Section 107(c)(4) modifies the application of Section 201(p), the revised definition of "new drug." Section 201(p) deals with drugs generically, not as individual products, and Section 107(c)(4) accordingly should be given the same generic meaning. Section 201(p) is not concerned with the rights of applicants, details of manufacture or other personal factors, as is Section 505, but with "[a]ny drug * * * the composition of which is such that such drug is not generally recognized, among experts * * * as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof" (A. 475). Because of its generic character, Section 201(p) permits manufacturers to market their own version of a drug which, generically, is not a new drug under this definition, without submitting to administrative preclearance by FDA, so long as the product's composition and labeling do not depart from the recognized generic categories.[28] On the other hand, if the product significantly departs from the accepted formulation, use, or method of administration, it becomes a "new drug" because it has deviated from the recognized generic standards.

Obviously, if the word "drug" in Section 201(p) were given an individual product, as opposed to generic, meaning, every new version or brand of every drug would be a "new drug" under the statute, since a particular brand would be unable to achieve the required general recognition and use until it had been marketed for some time. Thus, a non-generic inter-

[28] This has been FDA's interpretation since 1938. See 3 Fed. Reg. 3161, now codified at 21 C.F.R. 130.1(h) and (k).

pretation of the "new drug" definition would lead to the result that no drug product could be put on the market without going through administrative clearance proceedings. No one has ever supposed that the Act has this consequence. Since Section 107(c)(4) is addressed to the manner in which "the amendments to section 201(p) made by this Act" apply to "drugs," the word "drugs" should be given the same interpretation in both Sections.

2. A comparison of the language of Clause (C) of Section 107(c)(4) with that of related provisions of the Act supports the generic approach. In Clause (C), instead of describing exempted products in language turning on whether an NDA for any particular item was in effect, Congress used the broader formula "any drug * * * *not covered by* an effective application * * *" (emphasis added). This "covered by" language appears nowhere else in the Act, either in the original new drug provisions or in the Amendments. It contrasts with the more particularized language of Section 505(a), which was before Congress when the 1962 Amendments were under consideration and which clearly indicates that a new drug application thereunder is personal to the applicant and limited to the particular product upon which it is obtained. Specifically, former Section 505(a) prohibited any person from introducing any new drug into commerce "unless an application * * * * is effective with respect to such drug." And as petitioner recognizes (Br. 27–38), the other provisions of Section 505, and its consistent interpretation by the agency, establish that NDAs under that Section are personal to the manufacturer and particular to his product. If,

in Section 107(c)(4), Congress intended the application of Clause (C) to depend upon the particular status of individual products, it would presumably have used language like that in Section 505, rather than the "covered by" language it chose.

Moreover, this language in Clause (C) similarly differs from that used in the immediately preceding paragraph in the transitional provisions of the 1962 Amendments, Section 107(c)(3). The latter provision (which deals with the status of applications and expressly modifies Section 505) is plainly intended to apply to individual drug products, for it opens with the phrase "In the case of any drug *with respect to which* an application * * * is deemed to be * * * approved * * *." Congress' contrasting use of the phrase "covered by" in Clause (C) of Section 107(c)(4) therefore suggests that it intended to reach more than particular drug products with respect to which an application was in effect. The generic approach we suggest is consistent with that intent.

3. Our interpretation of the language Congress used in Section 107(c)(4) also comports with the regulatory scheme with which Congress was dealing when it enacted the 1962 Amendments. Me-too examples of a generic drug were in fact "covered by" the NDAs of the pioneers in a very real sense. In the ordinary case, particularly in the field of prescription drugs, an application was filed with FDA when a new compound was proposed for use in the treatment of a particular ailment or condition. If this "pioneer" NDA was allowed to become effective, the applicant was then free to market the product. Typically, several other manu-

facturers might file applications for their own examples of this generic drug. After the drug was on the market for a time, it would acquire the necessary general recognition and use to enable it to escape from the "new drug" category. Thereafter, anyone could market a me-too copy free of administrative premarketing regulation, provided his product conformed to the generically accepted formulation and labeling. Had the pioneers not obtained effective NDAs, the drug would not have acquired the necessary general recognition of safety and the required use experience for "not new drug" status, and the me-too products could not have been marketed lawfully without NDAs of their own.

Since the unregulated marketing of the me-too products in 1962 thus hinged on NDAs previously obtained by one or more other examples of the generic drug, the me-toos were, realistically, "covered by" the pioneer NDAs.[29] Thus, when the subject matter with which Congress was dealing in the 1962 Amendments is realistically considered, it is apparent that the words "covered by" were used in Section 107(c)(4) in a

[29] It is immaterial that there were instances in which a "me-too" product was actually marketed prior to the time an NDA became effective for any member of its generic class. Unless the product consisted entirely of substances known to be wholly innocuous and already in wide use for some purposes—which would be very unlikely in the case of a prescription drug (see Section 503(b) of the Act, 21 U.S.C. 353(b))—it was almost certainly a "new drug" under the 1938 Act, and its marketing was illegal without an effective application. If other members of its generic class subsequently obtained NDAs, and if by 1962 the generic drug was not "new" any longer, the me-too product was at the time the 1962 Amendments became effective "covered by" its brothers' NDAs.

sense broad enough to encompass all members of the generic class—regardless of whether the words "any drug" in that Section are also accorded a generic meaning.

4. The analysis adopted by both petitioner and the court of appeals depends almost entirely upon the fact that Section 505 addresses itself to drugs as individual products. We agree that an application under Section 505 is and always has been personal to the manufacturer who files it and particular to the product or products it names. But this is irrelevant for purposes of interpreting Section 107(c)(4), which modifies not Section 505 but Section 201(p), which is concerned with drugs in the generic sense.

Thus petitioner's contention that a generic approach to the interpretation of Section 107(c)(4) represents an about-face from prior agency interpretation is based on an erroneous premise which confuses the personal and individual requirements of Section 505 with the quite different purposes of Section 107(c)(4). In applying the latter provision, it is entirely irrelevant whether, as to any particular product belonging to a generic class for which an effective application was required, the agency may have issued a "not new drug" letter [30] or the manufacturer may have ceased complying with requirements under Section 505. Once the generic class of drugs had become generally recognized as safe, it would have been a pointless waste of the agency's limited resources to continue processing NDAs for new examples of the drug; similarly, if a

[30] Cf. *United States* v. *354 Bulk Cartons * * * Trim Reducing-Aid Cigarettes*, 178 F. Supp. 847, 853–854 (D.N.J.).

manufacturer with an effective NDA had ceased complying with filing, production, and reporting requirements under Section 505 and its implemening regulations, this was of no concern to the agency under the Act as it stood prior to 1962, since the product no longer required an active NDA.[31]

NDAs have been treated as personal under Section 505 in order to insure that administrative regulation of the composition, labeling, and manufacturing of drugs is maintained until such time as the drug attains general recognition of safety (and now effectiveness) and a sufficient history of actual use. It would be ironic indeed if this objective of maintaining administrative control over drugs, embodied in Section 505, were now to be turned by judicial interpretation into the instrument whereby FDA is denied the power to deal effectively with its congressionally assigned task

[31] From an administrative standpoint, however, the application could still be significant, for a product which had ceased to be a "new drug" could again become one in the light of new scientific knowledge. See *Upjohn Co.* v. *Finch*, 422 F. 2d 944 (C.A. 6). Drugs long and widely recognized by qualified experts as safe might subsequently prove to be dangerous in ways not perceived until after many years of use. Recent examples of this phenomenon include cyclamates to reduce sugar intake, see *Eisenstadt* v. *Finch*, CCH Food, Drug, and Cosmetic L. Rep. ¶ 40,392 (E.D.N.Y.), and hexachlorophene in antiseptic washing agents. In the case of hexachlorophene, the drug was originally subject to an effective NDA, and, after it became generelly recognized as safe, the NDAs became inactive and FDA issued "old drug" opinion letters. In light of recent data, the NDAs were reactivated. 37 Fed. Reg. 219, 20160. The reactivated NDA is important since, even though the product has lost its general recognition of safety, it may continue to be a useful drug when marketed under properly limited labeling subject to control by the new drug regulatory procedures of Section 505.

of removing pre-1962 drugs of unproven effectiveness from the Nation's drug counters.[32]

5. Petitioner errs in suggesting that the government's interpretation of Section 107(c)(4) would add nothing to what was already provided in the 1938 "grandfather" provision (Br. 60–63). (Even if petitioner were correct, such a result would be preferable to the arbitrary and discriminatory consequences flowing from petitioner's interpretation, under which the exemption in Section 107(c)(4) would be so broad as to consume almost entirely the provision for regulation enacted in Section 107(c)(3).)

Under the generic interpretation, the exemption is not available to any examples of a generic drug if

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[32] Petitioner attaches undue significance to the fact that Section 505(h) provides for judicial review of an NDA withdrawal only at the behest of the "applicant," contending that if Congress had intended to permit me-toos to be affected by withdrawal of the pioneer's NDA, it would have granted the me-too manufacturer the same avenue of judicial review (Br. 29). In order to ascribe weight to this factor as an indication of deliberate congressional intent, however, it is necessary to assume that Congress was specifically aware of the existence of large numbers of non-NDA'd me-too products and considered the regulatory significance of this fact in shaping the 1962 Amendments. As we have previously stated (see pp. 28–29, *supra*), there is no evidence in the legislative history of such awareness.

Me-too manufacturers are, moreover, subject to no injustice insofar as availability of judicial review is concerned. If one of the affected holders of an NDA seeks review in a court of appeals, the me-too manufacturer can intervene; if not, he can bring his own action for judicial review in a district court. The me-too manufacturer is, of course, also given full opportunity to participate in the administrative proceedings considering possible withdrawal of approval for the NDA. See our *Bentex* brief at p. 21.

the drug at any time between 1938 and 1962 was a "new drug," which status would be evidenced by the fact that some member of the generic class had obtained an NDA.[33] On the other hand, if the drug, viewed generically, had never been a "new drug," then no manufacturer's example of it would have been the subject of an effective application, and it would clearly have been, in the words of Senator Eastland (*supra*, p. 25), "an established drug which [had] never been required to go through the new drug procedures."

Petitioner's assumption that this construction gives no meaningful independent content to Section 107(c)(4) is perhaps due to its understandable focus on prescription drugs, into which category bioflavonoids fall. In Section 503(b), Congress identified a class of drugs which could be dispensed only upon a physician's prescription. Prescription drugs include any drug for human use which (A) is habit-forming; (B) "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the professional supervision of a practitioner licensed by law to administer such drug"; or (C) is limited to prescription use in the application under Section 505. Given the character of these drugs, it is indeed most unlikely that any could have come on the market subsequent to 1938 without being a "new drug" for some period of time.

[33] As pointed out in our brief in *Bentex* (p. 6), FDA early adopted the practice of turning back an application if it appeared that the product in question was not a new drug.

But the same is not true of over-the-counter drugs, which cover a broad range from cough drops and mouthwash to aspirin, skin ointments, and cold remedies. Many of these products consist entirely of ingredients long known to be safe or demonstrably without any significant biological or chemical activity (others, however, have in fact required and obtained NDAs). Such products, coming on the market for the first time between 1938 and 1962 but consisting of old, established ingredients, might well never have been subject to new drug regulation. They would, accordingly, be entitled to the exemption conferred by Section 107(c)(4) from efficacy regulation under the new drug procedures, so long as their composition and labeling remains unchanged.[34]

These exempted products would not necessarily have been "grandfathered" under the 1938 Act. If, for example, aspirin had been newly proclaimed after 1938 as a remedy for acne, this would have constituted a new labeling representation that would have permitted it to be deemed a "new drug" with respect to that claimed use under Section 201(p). Unless, however, the labeling recommended some increased dosage above the amounts specified and accepted for other uses of the drug, no safety question would have arisen and aspirin-for-acne would not in fact have been subject

[34] This is not to say that they would be generally immune from removal from the market for inefficacy, only that such removal would not be pursuant to new drug regulation. Such products would be subject to removal for misbranding if ineffective for their claimed uses, and they are considered by FDA to be subject for this reason to the procedures it has established for regulation of over-the-counter drugs by rulemaking, described in our *Bentex* brief (pp. 24–25).

to "new drug" regulation. Section 107(c)(4) would thus confer upon aspirin an exemption from "new drug" regulation for efficacy that was not available to it under Section 201(p).[35]

This approach is wholly consonant with what can be gleaned of the congressional intent from the legislative history. As indicated in our discussion of that history (p. 28, *supra*), Senator Kefauver, the principal sponsor of the 1962 Amendments, commented upon the bill's failure to subject "proprietaries now on the market" to the requirement that they support their claims for effectiveness. This statement came in the context of a comparison of the bill's impact on proprietary and prescription drugs, from which it may reasonably be inferred that he considered the latter to be subject to the effectiveness provisions.[36] Moreover, in light of Section 503's delineation of standards for prescription drugs, it may be presumed that Congress was aware that such drugs were very likely to have been at one time "subject to the new-drug procedure," while the comparatively less dangerous proprietaries were not as likely to have been so subject.

In short, petitioner points to no reason of public

[35] Any change in labeling after October 10, 1962, would, of course, subject the entire product to the 1962 Amendments. See *United States* v. *Allan Drug Corporation*, 357 F. 2d 713 (C.A. 10), certiorari denied, 385 U.S. 899.

[36] And in their separate statement of views attached to Part 1 of the Senate Report, Senators Dirksen and Hruska spoke approvingly of the exclusion from efficacy regulation of drugs that "are as familiar in the family medicine chest as aspirin or epsom salts" (p. 61), thus corroborating our view of the kinds of products Congress considered worthy of exemption and thought it was exempting.

policy or equity to support its position that it and other "me-too" manufacturers should be permitted to go on marketing drugs without demonstrating by adequately controlled scientific studies that they are effective as claimed. There is, by contrast, every reason to apply the effectiveness requirements of the 1962 Amendments to such drugs if the Amendments are meaningfully to achieve their basic purpose.

CONCLUSION

For the reasons stated, the judgment of the court of appeals should be affirmed on the grounds specified in this brief.

Respectfully submitted.

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APRIL 1973.

APPENDIX

This Appendix sets forth the findings reported by the NAS–NRC panels on USV's bioflavonoid products, which were reviewed by the Panel on Drugs Used in Hematologic Disorders and/or the Panel on Drugs Used in Metabolic Disorders. Reproduced here is the report of the former on "C.V.P. with Vitamin K" and of the latter on "Duo-C.V.P." Also reproduced is the report of the Panel on Drugs Used in Hematologic Disorders relating to Parke, Davis & Company's product "Rutin," a prominent bioflavonoid compound; this report contains additional observations regarding the panel's conclusions about the effectiveness of bioflavonoids.

C.V.P. With Vitamin K, NDA 9965, Log 734

PANEL ON DRUGS USED IN HEMATOLOGIC DISORDERS

INDICATIONS:

I. As a supplementary source of bioflavonoids, ascorbic acid, and menadione.

EVALUATION: Ineffective.

COMMENTS: The label correctly states that the dietary need for these agents has not been established, in agreement with Burns.

DOCUMENTATION:

1. Burns, J. J. Water-soluble vitamins; II. ascorbic acid (vitamin C), pp. 1673–1680. In L. S. Goodman and A. Gilman, Eds. The Pharmacological Basis of Therapeutics. (3rd ed.) New York: The Macmillan Co., 1965.

Approved by William H. Crosby,
Chairman.

DUO-C.V.P., NDA 9965, Log 733

PANEL ON DRUGS USED IN METABOLIC DISORDERS

INDICATIONS

None.

GENERAL COMMENTS

I. There is no package insert, but just a label indicating that this is a "supplementary source of bioflavonoids and ascorbic acid." There is no definite claim for therapeutic use and a statement on the label admits that "the need for bioflavonoids in human nutrition has not been established." However, the inference is that there is indeed a need for such a product. The references support this inference, in that everything from threatened abortion to bleeding gums is reported to have responded. The use of these materials as hemostatic agents for capillary fragility is felt to be unjustifiable and not proved. The Panel recommends that there should be a clear statement as to the use of this preparation.

II. The Panel finds that the term "minimum daily adult" requirement is meaningless because variations in nutritional needs depend on the health, sex, age, and physical activity of the individual. The term "dietary allowances" is preferred.

III. See the general statement on multiple-vitamin preparations.

Approved by D. H. NELSON,
Chairman.

RUTIN, NDA 6132, LOG 2407

PANEL ON DRUGS USED IN HEMATOLOGIC DISORDERS

INDICATIONS

I. Capillary permeability.

EVALUATION: Ineffective.

COMMENTS: Capillary permeability is normal, and should not be abolished. Moreover, data documenting bioflavonoid deficiency in man or supporting beneficial effects of this compound in bleeding states are insufficient to establish any clinical value for preparations containing rutin or allied compounds. The clinical value claimed in the literature is based on uncontrolled observations or poorly evaluated case reports. Any positive effects encountered may well have represented an unsuspected action of concurrently administered ascorbic acid. In 1955, a symposium was conducted on this subject at the New York Academy of Sciences, and Youmans, in his summarizing remarks, concluded on the evidence of the hemostatic value of the bioflavonoids: ". . . unfortunately, for one reason or another, they do not prove it, nor provide evidence of it." (2) A similar view is held by Burns, who states: "Proof that flavonoids are useful therapeutic agents is far from conclusive." (1)

DOCUMENTATION:

1. Burns, J. J. Water-soluble vitamins; II. ascorbic acid (vitamin C), pp. 1673–1680. In L. S. Goodman and A. Gilman, Eds. The Pharmacological Basis of Therapeutics. (3rd ed.) New York: The Macmillan Co., 1965.

2. Youmans, J. B. Summary of the clinical aspects of bioflavonoids and ascorbic acid. Ann. N.Y. Acad. Sci. 61:729–731, 1955.

Approved by WILLIAM H. CROSBY,
Chairman.

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-414

HYNSON, WESTCOTT & DUNNING, INCORPORATED,
Cross-Petitioner,

v.

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, AND DR. CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

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Section 201(p), 21 U.S.C. 321(p) 1, 2, 3, 4
Section 505(d), 21 U.S.C. 355(d) 1, 2, 3, 4
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The Drug Amendments of 1962, P.L. 87-781:

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REPLY BRIEF OF CROSS-PETITIONER HYNSON, WESTCOTT & DUNNING, INCORPORATED

ARGUMENT

I

The Existence Of Published Adequate And Well-Controlled Studies As A Prerequisite To A Finding Of General Recognition Of Safety And Effectiveness.

The Government contends that a showing of substantial evidence of effectiveness as defined in Section 505(d) of the Act is a condition precedent to a finding by experts under Section 201(p) that a drug is generally recognized as safe and effective and, therefore, not a new drug. We have shown in our main brief in this case (No. 72-414, pp. 21-28) that this proposed judicial amendment of the Act should be rejected. The legislative history and judicial precedent (Br. 15-19) and the

medical discourse on the necessity for controlled studies cited by the Government (App. A) do not support its position.

A. Legislative History.

The Government's recitation of testimony given at congressional hearings leading up to enactment of the Drug Amendments of 1962, is irrelevant. The interest of Congress and the experts testifying was in the type of evidence which the drug industry should be required to produce before a *new drug* should be permitted to be marketed. They were concerned with the marketing of new drugs without prior proof of effectiveness based upon adequate testing. We agree that Congress obviously intended that new drugs not be marketed without submission of substantial evidence as defined in Section 505 (d).

The question involved here, however, is not what type of evidence is required to prove the actual effectiveness of a new drug under Section 505 of the Act, but what evidence is required in order to bring a product within the new drug provisions of the Act, *i.e.*, evidence on the question of whether a drug is generally recognized as safe and effective under Section 201(p). The legislative history referred to in the Government's brief was not directed to this question and is, therefore, irrelevant.

B. The Cases Cited By The Government.

In its main brief in this case (No. 72-414), Hynson, Westcott & Dunning, Incorporated (HW&D) shows that the Government's attempt to graft the substantial evidence of effectiveness requirement in Section 505(d) to the jurisdictional test of new drug status in Section 201 (p) runs counter to a principle long-established in the case law: the question involved in determining whether

a drug is a new drug under Section 201(p) is not whether the drug is actually safe and effective but whether the drug is generally recognized as safe and effective by qualified experts (Br. 25-28).

The Government dismisses the authorities relied on by HW&D in a footnote in its brief (p. 23) and cites cases purporting to sustain its position. In actuality, the cases support HW&D's contention rather than the Government's. In each case the court pointed out that the question before it was not whether the drug *is* safe and effective, but whether it is generally recognized as safe and effective. *United States* v. *An Article Of Drug "Bentex Ulcerine"*, 469 F.2d 875, 879 (5th Cir. 1972); *United States* v. *41 Cases, More or Less*, 420 F.2d 1126, 1129 (5th Cir. 1970); *United States* v. *Article of Drug, Etc.*, 415 F.2d 390 (5th Cir. 1969), affirming 294 F. Supp. 1307, 1310 (D.Ga. 1968); *United States* v. *Article Of Drug . . . Mykocert*, 345 F.Supp. 571, 574 (D.Ill. 1972). The court in the case specifically relied on by the Government as supporting its position stated:

> "The statutory test for determining whether a drug is a "new drug" under 21 U.S.C. § 321(p) is whether the composition of the drug is generally recognized among experts qualified by their scientific training and experience to evaluate the safety and effectiveness of drugs as safe and effective for the uses prescribed, recommended or suggested in its labeling." *United States* v. *An Article of Drug . . . Xerac*, CCH Food, Drug, Cosmetic Law Reporter, ¶ 40,836 (No. 70-C-106, N.D. Ill.)

In any event, no court in any of the cases cited even mentioned the lack of substantial evidence test in Section 505(d) in connection with the general recognition test in Section 201(p). It is also significant to note that, as contrasted with the situation in the case at bar, litera-

ture on the drugs involved in the cases cited by the Government was either "virtually nonexistent" or completely lacking. *E.g., United States* v. *Article of Drug . . . Mykocert,* 345 F.Supp. 571, 575 (D.Ill. 1972). If Congress had intended that the substantial evidence test be read into Section 201(p), it could easily have said so.

II

The Right To A Hearing On The Question Of General Recognition Of Safety And Effectiveness.

The Government in its brief (No. 72-414) limits its argument to two questions, *viz.*, (1) whether substantial evidence of effectiveness in the medical literature consisting of adequate and well-controlled studies referred to in Section 505 (d) of the Act must exist before experts can determine if a drug is generally recognized as safe and effective within the meaning of Section 201 (p) of the Act; and (2) whether HW&D's drug, Lutrexin, is entitled to exemption from the effectiveness requirements of the Drug Amendments of 1962 by virtue of Section 107 (c) (4) thereof (Br. 8).

The Government thus completely ignores a basic contention of HW&D set forth in its main brief: assuming, *arguendo,* that substantial evidence of effectiveness as defined in Section 505(d) must be shown to exist in order to form a basis for experts to determine a drug to be generally recognized as safe and effective,[1] HW&D's affidavits and medical data (J.A. 32-72; 86-172), together with FDA's criticisms of them (J.A. 72), clearly show the existence of disputed issues of fact which, under fundamental principles of fairness and due process, should be resolved at a hearing (HW&D Br. in No. 72-414, 31-38).

[1] We show in Point I, *supra* and showed in our main brief (pp. 21-28), that this theory is not supported by the statute, its legislative history or judicial precedent.

The analysis of the affidavits and medical studies in our brief in No. 72-394 (pp. 14-25) further demonstrates that the evidence submitted to FDA in HW&D's request for a hearing (J.A. 24) raised genuine issues of fact as to whether HW&D has shown the existence of substantial evidence of effectiveness as defined in Section 505 (d) and as interpreted by FDA in its regulations (J.A. 487, 21 CFR 130. 12(a)(5)). The Government's statement (Br. 8) that HW&D ". . . contends that it is entitled to establish general recognition of safety and effectiveness under Section 201 (p) by means of evidence that would not suffice to satisfy the requirement of Section 505 . . ." is, therefore, clearly erroneous. HW&D's evidence cannot be dismissed as "uncontrolled clinical impressions" (Br. 13). The Government has made no attempt in its brief to refute HW&D's showing that its evidence raises disputed issue of adjudicative fact requiring a hearing. See *Goldberg* v. *Kelly*, 397 U.S. 254, 269-270 (1970).

HW&D is, therefore, entitled to a hearing on the new-drug status of Lutrexin and on the claims to exemption under 107(c) of the Drug Amendments of 1962. HW&D's affidavits and medical studies raise genuine issues of fact concerning the new-drug question and the exemption.[2]

III

Section 107(c) Of The 1962 Amendments.

A. The "Deemed Approved" Provision Of Section 107(c)(2).

The Government states that an NDA must remain "effective" even after the drug ceases to be "new" in order that FDA can retain the power to deal administratively with the contingency that doubt is cast upon the

[2] The status of HW&D's drug Lutrexin under FDA's "summary judgment" regulations is discussed in our brief in 72-394.

safety of a drug previously considered safe (Br. 27). We confess to bewilderment at this contention. If the Government were correct in its claim that an NDA remains "effective" even after the drug is no longer new and a question as to the safety of the drug should arise, the order withdrawing approval of the NDA could only be enforced by FDA in a judicial proceeding. This is precisely what FDA would have to do in order to challenge the safety of Lutrexin if our position is correct that, since Lutrexin was no longer "new" on October 9, 1962, its NDA was not "effective" on that date. There is no more reason for a continuing authority to withdraw an NDA for a drug which is no longer "new" than there is for such authority with respect to a drug which was never NDA'd because it was once generally recognized as safe but later was judged by FDA to be, in fact, not safe, upon the basis of new evidence.

Since no NDA for Lutrexin was "effective" on October 9, 1962, the drug was not "deemed approved." (For the same reason it was not covered by an "effective" application within the meaning of Section 107 (c) (4) (C)).

The Government refers to the provision of Section 107 (c) (2) that applications effective on October 9, 1962 would be "deemed approved", as a mere housekeeping measure." In our main brief (pp. 38-41), we discuss the meaning of this provision. We doubt that the use of a word so intimately linked to new drug procedures as is "effective", would be employed by the Congress as no more than a housekeeping device. Thus, an NDA for a new drug must be "effective" before the drug can legally be marketed. The term obviously has more meaning than the Government would give it.

It is also said by the Government that, if Lutrexin were not "deemed approved" the marketing of the drug would have been illegal since it could not claim approved

status under Section 107 (c) (2) and (3). On the contrary, it seems clear that only drugs "deemed approved" are subject to administrative withdrawal proceedings under either Section 107 (c) (3) or Section 505. Concededly, Lutrexin, though not "deemed approved," would be subject to the institution of judicial proceedings on the ground, *e.g.*, that it is a new drug because it is not generally recognized as effective. Only if it is also exempt under Section 107 (c) (4) would it be protected against a claim that it was a new drug without an approved application.

B. Section 107(c)(4).

The Government says that, despite the argument to the contrary in our main brief (p. 44), its interpretation of Clause (C) does, indeed, permit the exemption of over-the-counter drugs which, "as a generic class," were never subject to new drug regulations, even though they came on the market between 1938 and 1962, "because of universal recognition of the safety of their old, established ingredients" (Br. 27).

In its brief in *USV* (No. 72-666) the Government is less firm about the status of such drugs. It there states that such products "might well have never been subject to new drug regulation" (p. 51). This seems a more accurate suggestion as to the status of such products, particularly in the light of the new drug regulations of FDA which contemplate that almost any change in the active or inactive ingredients of a drug, or new combination of non-new drug ingredients, or new uses, or new dosages, may cause a drug to be "new".[3]

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[3] The pertinent provisions of the regulations follow (21 CFR 130.1)—

(h) The newness of a drug may arise by reason (among other reasons) of:

(1) The newness for drug use of any substance which composes such drug, in whole or in part, whether it be

The Government's argument does not square with the provision of Section 130.1(h)(4) relating to new uses of drugs which are not new drugs when promoted for other uses. This regulation reflects a long-standing policy of FDA which was followed before the enactment of the effectiveness provisions of the 1962 Amendments.[4] It seems clear that any new combination of "old" ingredients would be subject to new drug procedures, even before 1962, as well as any new use or dosage and would continue to be so subject until they became generally recognized as safe and had been used to a material extent and for a material time. The Government has not, we submit, substantiated its argument that it has not, in effect, read Section 107(c)(4) out of the 1962 Amendments.

Nor is there any evidence that the addition of the requirement of effectiveness to Section 201(p) elim-

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an active substance or a menstruum, excipient, carrier, coating, or other component.

(2) The newness for drug use of a combination of two or more substances, none of which is a new drug.

(3) The newness for drug use of the proportion of a substance in a combination, even though such combination containing such substance in other proportion is not a new drug.

(4) The newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body.

(5) The newness of a dosage, or method or duration of administration or application, or other condition of use prescribed, recommended, or suggested in the labeling of such drug, even though such drug when used in other dosage, or other method or duration of administration or application, or different condition, is not a new drug.

[4] The provision relating to newness of drugs including new uses of old drugs was in effect in 1956, long before effectiveness requirements were added in 1962. See Section 130.1(f)(4) of 21 CFR, revised as of January 1, 1963.

inated a Section 107(c)(4) exemption for Lutrexin, as the Government contends (Br. 23 et seq.). It must be remembered that Section 107(c)(4) was not in S.1552 when it was first reported to the Senate before the addition of "effectiveness" to Section 201(p).[5] It is, therefore, not apparent how, as the Government states, Lutrexin could have been "grandfathered" without the transitional provisions, including Section 107(c)(4), had been adopted. In any event, that section should be interpreted on the basis of the statute as enacted, and not, as the Government would have it, on the basis of different provisions in an earlier bill.

The addition of "effectiveness" to Section 201(p) was hardly as significant, in this connection, as the Government suggests. The basis assigned for such addition was "to eliminate any possible ambiguity" on the question "as to the circumstances and extent to which a new claim or change of claim for effectiveness made after the initial approval of a new drug application could be made without supporting evidence to be submitted to the Department under the new drug procedure."[6]

We submit, therefore, that in view of this expression of the Senate Committee and the discussion in our main brief, the Government is wrong when it states "this history thus establishes that Congress abandoned its original inclination to exempt 'safe' pre-1962 drugs from the new drug effectiveness requirements . . ." (Br. 31).

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[5] S. Rep. 1744, Part 2, 87th Cong., 2nd Sess., p. 7.

[6] *Id.* at 5.

CONCLUSION

For the foregoing reasons and the reasons stated in our brief in No. 72-394 and in our main brief in this case (No. 72-414), (1) the decision of the Court of Appeals that HW&D was entitled to a hearing on the question of whether there is substantial evidence of effectiveness of Lutrexin should be affirmed; (2) the NDA for Lutrexin was not "deemed approved" under the provisions of Section 107(c)(2) of the Drug Amendments of 1962 and was therefore not subject to *administrative* withdrawal proceedings under Section 505(e)(3) of the Act as amended; (3) the drug is entitled to the exemption from *any* proceedings based on the *effectiveness* requirements of the 1962 Amendments by reason of Section 107(c)(4); and (4) HW&D is entitled to an evidentiary hearing before FDA on the jurisdictional questions of whether Lutrexin was "deemed approved" and therefore not subject to administrative withdrawal proceedings under Section 505(e)(3), whether it was exempt under Section 107(c)(4), and whether it is now generally recognized as both safe and effective and not subject to Section 505.

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In the Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-394

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION, AND WELFARE, ET AL., PETITIONERS

v.

HYNSON, WESTCOTT AND DUNNING, INCORPORATED

Nos. 72-414, 72-528, 72-555, 72-666

AND CONSOLIDATED CASES

ON WRIT OF CERTIORARI TO THE UNITED STATES COURTS OF APPEALS FOR THE THIRD AND FOURTH CIRCUITS

CONSOLIDATED REPLY BRIEF FOR THE FEDERAL PARTIES

Taken together, the industry briefs filed in these five cases would severely undermine the drug effectiveness provisions of the Act. The proposed impact of these industry briefs may be seen by examining collectively the following propositions for which they contend:

(1) In spite of the fact that the statutory standard for withdrawal of approval of an NDA, as with initial denial of approval, turns on the "lack" of sub-

stantial evidence of effectiveness (rather than requiring FDA to determine that the drug is in fact ineffective), once an NDA has been approved, the burden shifts to the agency to justify removal of the product from the market (although all the information relevant to the inquiry is in the possession of the manufacturer).[1]

(2) Even after the National Academy of Sciences-National Research Council, under contract with FDA, has found wholly inadequate support for the effectiveness of a drug, the FDA's own review has confirmed this evaluation, and neither the manufacturer nor any other interested person has identified substantial evidence of effectiveness, FDA must in some way come forward with additional information on its own before it may require the manufacturer to come forward with his evidence of effectiveness.[2]

(3) All that a manufacturer need do to obtain a hearing on withdrawal of an NDA is to make conclusory allegations sufficient, if proved, to present a factual issue, and FDA may not properly pierce those allegations to determine whether there is any basis whatever for them.[3]

(4) Withdrawal of NDA approval by FDA through the administrative process is largely academic anyway, because the manufacturer is thereafter free to relitigate basically indistinguishable issues *de novo* in

[1] Hynson Br., No. 72-394, pp. 39-41; PMA Br. 12-13; Squibb Br. 13-14.

[2] *Ibid.*

[3] Hynson Br., No. 72-394, pp. 42-43; PMA Br. 3-4, 22.

a district court in contending that the product is no longer a "new drug."[4]

(5) Even though the notice of proposed NDA withdrawal explicitly states that it applies to all me-too drugs, in fact all of those me-too drugs are free to ignore the administrative process and may thereafter relitigate all of the identical issues *de novo* in a district court.[5]

(6) In any event, the entire 1962 Amendments and the NDA withdrawal procedure apply only to the relatively few (no more than 4,000) products which shouldered the burden of complying with administrative regulatory procedures by obtaining an NDA during the 1938–1962 period, and not to the vast majority of the estimated 35,000 prescription and 100,000 to 500,000 OTC drugs now on the market.[6]

(7) Not only is the "no longer new drug" issue separable, to be relitigated *de novo* in district courts by every manufacturer, but all that need be shown to satisfy this exemption from the regulatory requirements of the Act is the very type of anecdotal opinion that Congress, after informed consideration, explicitly rejected as scientifically inadequate to demonstrate the effectiveness of drugs.[7]

(8) FDA is powerless to utilize any administrative procedure whatever, whether rulemaking, adjudication, or a combination of the two, to settle initially any issue of drug safety or effectiveness, except when

[4] CIBA Br. 6–14; PA Br. 73–75; PMA Br. 26–41.
[5] Bentex Br. 8–20; PA Br. 65–73, 75–77; PMA Br. 26–41.
[6] PA Br. 50–64; PMA Br. 41–54.
[7] Bentex Br. 6–7; PMA Br. 32–34.

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explicitly asked by the industry to do so in an individual case. It must resort directly to court enforcement in every instance rather than asserting its primary jurisdiction as the expert government agency on the safety and effectiveness of drugs.[8]

These briefs state that, whatever good intentions Congress might have had in enacting the 1938 Act and the 1962 Amendments, it simply failed to use sufficiently clear statutory language to effectuate its purposes, and therefore the matter must be referred back to Congress to repair the damage. Surely, Congress did not intend the narrow construction placed upon the Act or the constricted power attributed to FDA in these industry briefs. Both the statutory language and the legislative history make that clear. Nor can the industry advance any public policy for its proposed debilitation of the Act and of the agency's authority to implement it.

I. FDA Has Administrative Authority To Deal With a Broad Range of Drug Safety and Effectiveness Issues

At the heart of all five cases is the industry's attempt to limit FDA's authority to processing the specific NDAs which have been submitted to it and bringing lawsuits in the district courts to litigate the status of all other drugs. This approach would strip the agency of any real authority to accomplish the mandates laid down in the Act by Congress. Moreover, the powers attributed to FDA in the industry briefs

[8] PA Br. 21–49, 54–61; PMA Br. 34–41.

would be substantially smaller than those exercised by other administrative agencies. Since Congress has given broad and sweeping powers to many federal agencies dealing with purely economic matters, as this Court has recognized in numerous cases,[9] there is no reason why it would have intended to deny comparable authority to the agency entrusted with primary responsibility for protecting the health and safety of the nation with respect to drugs.

A. FDA HAS THE AUTHORITY TO DETERMINE, IN THE FIRST INSTANCE, ISSUES OF DRUG SAFETY AND EFFECTIVENESS

It is accepted practice that when dealing with problems whose dimensions go beyond a particular case and implicate an entire industry or major segments thereof, regulatory agencies are not required to operate on a narrow, case-by-case basis, but have authority to—and do—deal with them as broadly as necessary. The reason is obvious. Administrative agencies are created because of the need to apply expert knowledge and experience to particular segments of society or particular forms of conduct that have their own specialized problems and characteristics. The application of that expertise may indicate to the agency that a particular problem can be effectively solved only through comprehensive remedies. If, for example,

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[9] *E.g.*, *F.T.C.* v. *Colgate-Palmolive Co.*, 380 U.S. 374, 384–385 (F.T.C.); *United States* v. *Midwest Video Corp.*, 406 U.S. 649, 662–665 (F.C.C.); *American Power & Light Co.* v. *S.E.C.*, 329 U.S. 90, 112, and *S.E.C.* v. *Chenery Corp.*, 332 U.S. 194, 202–204 (S.E.C.); *N.L.R.B.* v. *Seven-Up Bottling Co.*, 344 U.S. 344, 346–347 (N.L.R.B.).

the public interest requires that a drug be removed from the market because it is unsafe or ineffective, the public would not be adequately protected if the only way FDA could do so would be by bringing 20 separate proceedings against each manufacturer of an example of the drug. The problem can properly be solved only by permitting FDA to act against the drug through a single proceeding in which each of the manufacturers involved could be heard.

This Court has recognized the authority of administrative agencies to deal with broad-scale problems on a broad enough basis for their effective solution. In *United States* v. *Storer Broadcasting Co.*, 351 U.S. 192, the Court upheld the rules of the Federal Communications Commission limiting the number of broadcasting stations a single individual may own as a proper exercise of the agency's "rule-making authority necessary for the orderly conduct of its business" (*id.* at 202). The Commission, of course, could have dealt with the problem of concentration of control in the broadcasting industry on a case-by-case basis. That is, instead of deciding that no individual could own more than five television stations, it could have determined appropriate limitations for each owner in separate proceedings concerning only that owner and the particular stations involved. This Court held, however, that its broad regulatory responsibilities authorized the agency to deal with the problem on a comprehensive basis.

FDA similarly is properly exercising its broad authority to protect the public from ineffective drugs by

dealing with the problem in the only practical way—through proceedings designed to prevent marketing of generic categories of drugs that do not satisfy the statutory standard. All manufacturers of each drug have full opportunity in these proceedings to show that the generic drug itself or their particular form of it is effective. There is no reason in fairness or precedent for requiring the agency to engage in protracted case-by-case district court litigation in which it would be required to prove the same thing over and over again, with respect to each manufacturer of what is essentially the same product.[10]

FDA has undertaken to implement the effectiveness requirements of the 1962 Amendments by two procedures designed to deal with these issues on a broad industry-wide basis. First, it has consistently taken the position—and has so advised the industry in every proceeding—that any withdrawal of NDA approval, (whether for a prescription or OTC drug) covers all me-too drugs.[11] Second, it has established administrative procedures to determine, in the first instance, the safety and effectiveness of OTC drugs,[12] and, depend-

[10] This Court stated in *S.E.C.* v. *Chenery Corp.*, 332 U.S. 194, 203, that "the choice between proceeding by general rule or by individual, *ad hoc* litigation is one that lies primarily in the informed discretion of the administrative agency."

[11] As in all the government briefs, a "me-too" drug includes all identical, similar, and related drugs, as defined at 37 Fed. Reg. 23185, which added Section 130.40 to 21 C.F.R.

[12] In the interest of fair play, FDA has proposed to defer implementation of the 1962 Amendments through withdrawal of NDA approval of over four hundred 1938–1962 OTC drugs until

ing upon the outcome of the present cases, intends to develop a similar procedure for settling the status of prescription drugs. These two approaches stand on basically the same legal footing—FDA's authority to engage in administrative regulation that comprises both adjudication and rulemaking. The industry briefs uniformly contend that both are unlawful and that FDA can decide these issues only with respect to those drugs for which an individual NDA has been filed with the agency for a specific drug product.[13]

In an NDA withdrawal proceeding, Section 5(e) of the Administrative Procedure Act, 5 U.S.C. 554(e), permits FDA to issue a declaratory order governing all drugs covered by that NDA. Section 701(a) of the Act broadly authorizes FDA "to promulgate regulations for the efficient enforcement of this Act," [14] subject of course to the notice-and-comment rulemaking procedure.

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after the comprehensive OTC drug review is completed. 37 Fed. Reg. 7807; see para. XV of the order entered in *American Public Health Assn.* v. *Veneman*, 349 F. Supp. 1311 (D.D.C.), 37 Fed. Reg. 26623, 26624. If FDA has no authority to determine the safety and effectiveness of OTC drugs through its current review procedures, 37 Fed. Reg. 85, 9464, the agency must proceed to withdraw those NDAs and to bring enforcement action against all me-too products.

[13] Br. for the Proprietary Association ("PA"), pp. 21–49, 54–61; PMA Br. 34–41.

[14] A similar broad authorization "to promulgate such rules and regulations as are necessary to carry out the provisions of this chapter" under the Poultry Products Inspection Act has been construed as "a general legislative power concerning matters covered by the Poultry Act *in addition* to whatever adjudicative power is conferred by particular provisions thereof." *Borden Co.* v. *Freeman*, 256 F. Supp. 592, 598 (D. N.J.). The PA Brief (pp. 39–41) and the PMA Brief (p. 29) argue that the provision for rulemaking after a "public hearing" in Section

PMA contends (Br. 35–36) that FDA has no authority to issue a declaratory order under the Administrative Procedure Act determining whether a drug is a "new drug" because that procedure is available to an agency only for "questions which it is otherwise authorized to adjudicate on the record of a hearing." The argument, of course, assumes the question at issue, *i.e.*, does FDA have authority in its administrative proceedings to determine whether a drug is a new drug? Section 5 of the Administrative Procedure Act, 5 U.S.C. 554, of which the provision authorizing declaratory orders is a part, primarily prescribes certain procedures that an agency must follow "in every case of adjudication required by statute to be determined on the record after opportunity for an agency hearing." Section 5(e), however, states that the agency "in its sound discretion, *may* issue a declaratory order to terminate a controversy or remove uncertainty" (emphasis added).

This provision *authorizes* an agency to issue declaratory orders in all cases of formal adjudication to which Section 5 applies, but it is not *limited* to that

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701(e) of the Act for certain specified types of regulations precludes use of the general rulemaking authority in Section 701(a) of the Act for other types of regulations. Congress has not required a public hearing for all FDA regulations, and FDA has in fact promulgated hundreds of substantive regulations under Section 701(a) which, as this Court has recognized, "have the status of law." *Abbott Laboratories* v. *Gardner*, 387 U.S. 136, 151–152. See also, *Pfizer, Inc.* v. *Richardson*, 434 F. 2d 536, 544 (C.A. 2), where Section 701(a) is characterized as granting "rule-making powers." Cf. *United States* v. *Allegheny-Ludlum Steel*, 406 U.S. 742, 757.

situation. Rather, it gives the agency broad discretion to issue a declaratory order whenever appropriate "to terminate a controversy or remove uncertainty." See *First Savings and Loan Association of the Bahamas, Ltd.* v. *Securities and Exchange Commission*, 358 F. 2d 358, 360 (C.A. 5), ruling that the Commission has authority under that provision to issue a declaratory order determining whether a foreign organization is exempt from the registration provisions of the Securities Act of 1933, even though the latter Act does not provide for adjudication on the record after opportunity for hearing of exemptions from its coverage. Similarly, FDA may issue a declaratory order to terminate a controversy or remove uncertainty over whether a particular drug is a "new drug" that is subject to the requirements of Section 505 of the Act.

In sum, therefore, in accordance with the admonition of the courts that "* * * agencies must exert the greatest resourceful, imaginative ingenuity in devising procedures which in a day of ever-expanding dockets will permit the regulatory process to function properly with reasonable dispatch," [15] it is well within the agency's authority to fashion administrative procedures designed to enforce the 1962 Amendments in the most direct and efficient manner consistent with fair play.

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[15] *F.T.C.* v. *J. Weingarten, Inc.*, 336 F.2d 687, 691–692 (C.A. 5). FDA's OTC drug review procedures have been regarded by one court as "calculated to achieve precisely the result applauded by the Fifth Circuit Court of Appeals in *Weingarten*," *United States* v. *Articles of Food and Drug* * * * *Coli-Trol 80 Medicated*, CCH Food, Drug, Cosmetic L. Rep., para. 40,837 (N.D. Ga.).

Indeed, even under the more primitive Food and Drug Act of 1906, this Court stated:

> Congress may declare its will, and, after fixing a primary standard, devolve upon administrative officers the "power to fill up the details" by prescribing administrative rules and regulatons. * * * [*United States* v. *Shreveport Grain & Elevator Co.*, 287 U.S. 77, 85.]

More specifically, in *Moog Industries, Inc.* v. *F.T.C.*, 355 U.S. 411, 413, this Court noted the responsibility of an administrative agency, in its discretion, "to develop that enforcement policy best calculated to achieve the ends contemplated by Congress," and in *F.T.C.* v. *Universal-Rundle Corp.*, 387 U.S. 244, 251, it admonished that such discretion does not include "unbridled power to institute proceedings which will arbitrarily destroy one of many law violators in an industry." [16] Yet in the instant cases the industry briefs argue that FDA *must* proceed on a case-by-case basis and is precluded from fashioning administrative adjudicatory and rulemaking procedures that will avoid the inequities that necessarily result from that approach.

B. MEANINGFUL DRUG EFFECTIVENESS REGULATION CANNOT BE ACCOMPLISHED BY DE NOVO CASE-BY-CASE LITIGATION

The industry briefs argue that litigation with respect to the safety and effectiveness of a drug, including the new drug status of a product, is a simple and

[16] See also *Columbia Broadcasting System* v. *United States*, 316 U.S. 407, 421.

straightforward matter, and thus entirely appropriate for the courts. In fact, however, such litigation is invariably protracted, it involves an enormous expenditure of government, industry, and court resources; it potentially includes so many products and issues that it would be impossible to make a substantial dent in the agency's task of removing ineffective drugs from the market by this means; it necessarily discriminates among competing products, because not all can be the subject of a court enforcement proceeding at one time; it promotes a lack of uniformity of results by having similar issues resolved by different courts; and in the end it fails to settle any issue because of the possibility of immediate product reformulation by the manufacturer, requiring new litigation.

The inadequacy of case-by-case judicial proceedings has been brought home forcefully by experience. FDA initially attempted through case-by-case litigation to apply the effectiveness requirements of the 1962 Amendments to products for which no NDA has been filed. It brought seizure actions against a few products [17] on the grounds that they were illegal new drugs marketed without an NDA and that they were misbranded. Just this handful of cases required a large expenditure of governmental manpower to prepare and present the necessary medical testimony. The typical case required obtaining affidavits or live testimony from between five and fifteen expert medical

[17] *E.g.*, Cetacaine Topical Anesthetic, Bentex Ulcerine, Chaser for Hangover, Mycocert, Mornin' Afta, Vice Spice, Xerac Alcohol Acne Gel, Asper-Sleep, Ornex, and Excedrin PM.

witnesses, often full professors or deans of medical schools. It became clear that FDA was incapable of a caseload of more than perhaps ten or fifteen such cases in any year, because of the heavy workload involved.

Moreover, this case-by-case approach is inherently unfair, because it requires compliance with the law by one manufacturer while his competitors remain free to violate it. Whether an NDA withdrawal proceeding or a court enforcement action is involved, FDA does not have the resources to institute the same action against all competing manufacturers of identical, similar, or related products unless all those products can be brought before the agency in an administrative proceeding at the same time.[18] In one recent instance involving court enforcement action brought by the agency, for example, the company argued that FDA had unfairly singled out its product. It pointed out (and FDA agreed) that there were at least 1200 competing products against which no action had been instituted.[19] The manufacturers of products whose NDAs have been withdrawn by the agency in the past three years have similarly complained bitterly to FDA that non-NDA'd me-too products still remain on the market.

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[18] See 37 Fed. Reg. 85–86.

[19] The product was seized by FDA. *United States* v. *An Article of Drug * * * Ornex Capsules*, No. 223–71 (D.N.J.). The company then brought an independent proceeding in a different court to enjoin FDA from taking further action against its product. *Smith Kline & French Laboratories* v. *Richardson*, No. 71–387 (E.D. Pa.).

Moreover, it rapidly became apparent that court enforcement actions frequently would settle little or nothing. In the *Xerac* case, for example, the government prevailed, after a protracted trial.[20] While the case was pending on appeal, however, the company's attorney informed FDA that it was reformulating the product. The issue then on appeal thus became largely academic, and FDA was faced with the choice of either beginning the litigation anew, with the realization that if it prevailed the company might again reformulate, or dropping the matter.[21]

FDA not only found such litigation costly, time-consuming, and unproductive, but increasingly found it difficult to obtain expert witnesses on the often trivial issues involved. It is not easy, for example, to obtain the time and services of a truly expert pharmacologist to testify that a fake aphrodisiac is in fact ineffective.[22]

On the other hand, the agency has been very successful in attracting the time and talent of the country's leading experts on drug safety and effectiveness in reviewing and developing broad standards for all products falling within a class, both in the completed NAS-NRC review and in the current re-

[20] *United States* v. * * * "*Xerac Alcohol Acne Gel*," CCH Food, Drug, Cosmetic L. Rep., para. 40,836 (N.D. Ill.).

[21] It is as a result of this experience that FDA elected to establish an administrative procedure (described in the government's *Bentex* brief, pp. 24–25) and has abandoned recourse to such useless litigation.

[22] *United States* v. *An Article of Drug* * * * *Vice Spice*, Civ. No. 35904 (E.D. Mich.).

views of OTC drugs, biologics, and diagnostic products. The major public benefits from such an approach are already being demonstrated in the OTC drug review.[22]

The industry briefs appear to take the position that FDA may impanel such experts to make determinations on safety and effectiveness, but that those determinations have no legal effect whatever. If those determinations could accomplish nothing more than to establish FDA's priorities for bringing enforcement

[22] The first proposed monograph for an OTC drug class of products, covering antacids, has recently been published. 38 Fed. Reg. 8714–8724. The manufacturers have already had an opportunity for a hearing before the expert panel that made the initial report, now have an opportunity for comment on the proposal, and will later have an opportunity for a further hearing before the Commissioner and for court review. 37 Fed. Reg. 85, 9464. The enormous amount of work that went into this proposal, and the potential benefit to the public as a result, are apparent on its face. If FDA were limited to implementing the NAS-NRC evaluations of the nineteen 1938–1962 NDAs that existed for OTC antacids (37 Fed. Reg. 7824–7827) and to bringing district court actions against unlawful drugs, as the Fourth Circuit held in *Bentex* and the industry briefs argue, and could not exercise primary jurisdiction over the subject matter to determine the issue initially through the administrative process (subject, of course, to judicial review), that notice and the entire OTC review procedure would be a nullity. The industry argues, indeed, that the only lawful purpose that can be attributed to such an administrative proceeding is to permit the agency to determine which lawsuits it will in fact file in the future. In short, each of the issues dealt with in this initial Federal Register notice for antacids would, in the event of substantial industry non-compliance, be required under this view to be relitigated *de novo* in district courts throughout the United States.

actions in the courts, however, the usefulness of such an administrative procedure—whether it involves withdrawal of an NDA for a drug (including all me-too versions) or determination of the safety and effectiveness of a class of drugs—would obviously be destroyed, and the doctrines of primary jurisdiction and exhaustion of administrative remedies would become meaningless in the field of drug regulation by the expert agency established for the purpose by Congress. While courts obviously must have the ultimate authority to determine the reasonableness of any rulemaking or adjudication undertaken by an administrative agency, the notion that such adjudication or rulemaking can do no more than assist the agency in establishing its court enforcement priorities undermines the ability of the agency to carry out its statutory responsibilities.

II. Hynson Was Not Improperly Denied a Hearing on Withdrawal of Lutrexin's NDA

The industry briefs, in discussing the issue raised by the government's petition in *Hynson* (No. 72–394), argue that a manufacturer is entitled to an evidentiary hearing on withdrawal of his NDA, as a matter of right, whenever he alleges the existence of adequate and well-controlled clinical studies, and that neither FDA nor a court may pierce those allegations to determine whether, on its face, the evidence proffered in fact may satisfy the requirements for an adequate and well-controlled clinical study as defined in the Commissioner's regulations. These briefs also urge,

on the basis of a recent decision of the District of Columbia Circuit, that FDA has the burden both to come forward with evidence to show a lack of effectiveness and to prove a lack of effectiveness before approval of an NDA may be withdrawn. They suggest that the lack of hearings to date and the fact that FDA is not an independent arbiter show the unfairness of the procedure followed by the agency. Finally, Hynson argues that it is entitled to a hearing because the FDA summary judgment regulations were adopted after it initially requested a hearing; it also contends that the evidence it presented is sufficient to justify a hearing if analyzed on the basis of "historical controls."

A. CONCLUSORY ALLEGATIONS THAT ADEQUATE, WELL-CONTROLLED STUDIES EXIST DO NOT SUFFICE TO REQUIRE A HEARING

Hynson argues flatly that Section 505 requires a hearing "if the applicant requests a hearing" (Br. 42).

The Pharmaceutical Manufacturers Association ("PMA"), although paying lip service to the proposition that no evidentiary hearing is required in the absence of a dispute over a material fact (Br. 11), empties the concept of significant meaning by asserting (Br. 20):

> Where the manufacturer offers the opinion of a qualified expert that a certain study or group of studies meets the criteria for an "adequate and well-controlled investigation" and establishes the effectiveness of a product, a genuine factual dispute is presented. That dispute can

> be resolved only through confrontation and cross-examination at an evidentiary hearing. * * *

Any manufacturer can allege—and, indeed, virtually always can find at least one physician to submit an affidavit in support of its contention—that adequate and well-controlled studies exist. If such an allegation suffices to require a hearing even though the studies, on their face, are clearly defective, hearings would, as a practical matter, be required on request.

Thus, the question is whether FDA is bound by the manufacturer's conclusory allegations in determining whether a hearing is appropriate, or whether it may look behind those allegations to determine whether the detailed requirements for an adequate and well-controlled clinical study set forth in the regulations are even possibly satisfied by any of the materials submitted to show effectiveness.

It is now well-established, in the judicial summary judgment context, that the trial judge is permitted, and indeed expected, to go behind the pleadings to determine whether an alleged issue of fact is real or imagined.[24] If the court deter-

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[24] *Kern* v. *Tri-State Insurance Co.*, 386 F.2d 754 (C.A. 8); *Robin Construction Co.* v. *United States*, 345 F.2d 610 (C.A. 3); *Perma Research & Development Co.* v. *Singer Co.*, 410 F.2d 572 (C.A. 2); *Bland* v. *Norfolk & Southern R.R. Co.*, 406 F.2d 863 (C.A. 4); *J. W. Scarboro, Jr.* v. *Universal C.I.T.*, 364 F.2d 10 (C.A. 5); *McKinney* v. *Armco Steel Corp.*, 270 F. Supp. 360 (W.D. Pa).

Rule 56 of the Federal Rules of Civil Procedure provides in pertinent part:

> **(e) Form of Affidavits; Further Testimony; Defense Required.** * * * When a motion for summary judgment is

mines, upon scrutiny of the affidavits, that the allegation is unsupportable and that there is actually no disputed material fact, summary judgment is of course permissible. This principle has been applied to FDA's summary judgment withdrawal proceedings in all cases except *Hynson. Upjohn Co.* v. *Finch,* 422 F.2d 944 (C.A. 6); *Pfizer, Inc.* v. *Richardson,* 434 F. 2d 536 (C.A. 2); *American Cyanamid* v. *Richardson,* 456 F. 2d 509 (C.A. 1); *Bristol Laboratories* v. *Richardson,* 456 F.2d 563 (C.A. 1); *Pharmaceutical Manufacturers Ass'n* v. *Richardson,* 318 F. Supp. 301 (D. Del.).

In the instant case, the conclusory assertions submitted by Hynson regarding the scientific adequacy of

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made and supported as provided in this rule, an adverse party may not rest upon the mere allegations or denials of his pleading, but his response, by affidavits or as otherwise provided in this rule, must set forth specific facts showing that there is a genuine issue for trial. If he does not so respond, summary judgment, if appropriate, shall be entered against him.

The "Notes of Advisory Committee on Rules," 28 U.S.C.A. following Rule 56, state as to this provision:

> The last two sentences are added to overcome a line of cases * * * which has impaired the utility of the summary judgment device. * * *
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> * * * * *
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> The very mission of the summary judgment procedure is to pierce the pleadings and to assess the proof in order to see whether there is a genuine need for trial. * * *
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> * * * * *
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> It is hoped that the amendment will contribute to the more effective utilization of the salutary device of summary judgment.

its studies do not overcome the plain fact that the studies themselves, on their face, fail in numerous respects to meet the criteria of the regulations. There is thus no basis for relying upon the face of the affidavits, as the Fourth Circuit did in this case, and ignoring the Commissioner's analysis of the defects in the underlying data submitted to support those affidavits.

B. IT IS ENTIRELY FAIR AND REASONABLE TO PLACE THE BURDEN ON THE NDA HOLDER TO COME FORWARD WITH A SHOWING THAT ADEQUATE STUDIES MAY EXIST

The industry briefs present a confusing description of the procedure used by FDA to withdraw NDA approval and are divided on the issue whether the *Hynson* case fully presents all of the issues inherent in that procedure. A review of the exact procedure used and the issues it presents to this Court is therefore appropriate.

In all of the cases now before this Court, the proceeding began with the receipt of an NAS–NRC evaluation of the drug in question. This evaluation was furnished to the manufacturer and was made known and furnished to all other manufacturers and to the public through a Federal Register notice, with a request for submission of any additional information that might establish the drug's effectiveness. On the basis of the information contained in the NDA file, any data submitted by the company to the NAS–NRC, the NAS–NRC report, and any additional information submitted by any person, the Commissioner

then made his own determination regarding withdrawal of the NDA, and if he decided tentatively that approval should be withdrawn, published an appropriate notice of opportunity for hearing in the Federal Register. The basis of this tentative determination was the conclusion of the NAS–NRC panels, showing a lack of substantial evidence of effectiveness, together with the absence of such a showing in any other materials then before the Commissioner.

The notice of opportunity for hearing provides thirty days within which the manufacturer or any other interested person may request a hearing. Under 21 C.F.R. 130.14(a) (J.A. 490), the manufacturer is entitled, upon request, to an explanation of the reasons for the Commissioner's proposed action. Hynson made no such request and cannot now complain, after failing to take advantage of this provision, that it should at that stage have received a fuller explanation of the Commissioner's reasons.

Under 21 C.F.R. 130.14(b) (J.A. 491), a request for a hearing must contain an organized, factual analysis identifying the existence of adequate and well-controlled clinical studies in order to show a genuine issue of fact on which the hearing might be held. In *Hynson,* a request for a hearing was made and the Commissioner carefully evaluated each of the scientific studies identified by Hynson to support effectiveness. The results of the Commissioner's evaluation, which showed that no adequate and well-controlled study was presented, were published in the Federal Register, and the hearing was denied. No

request for reconsideration of the Commissioner's determination was made.[25] The government believes that all aspects of this procedure are fully at issue in the *Hynson* case.[26]

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[25] If Hynson concluded that the Commissioner's evaluation was erroneous, it could have petitioned for reconsideration, and the Commissioner could then either "revoke" his order and "reinstate such approval" in accordance with Section 505(f) of the Act, or order a hearing, or take any other appropriate action justified by the petition. While the Commissioner's hearing regulations do not specifically provide for petitions for reconsideration, such petitions would be entertained. An administrative agency may, in its discretion, reopen any proceeding for reconsideration. *United States* v. *Pierce Auto Lines*, 327 U.S. 515, 534–535; *I.C.C.* v. *Jersey City*, 322 U.S. 503, 517–518; *Tagg Bros. & Moorhead* v. *United States*, 280 U.S. 420, 444–445; *American Chain & Cable Co.* v. *F.T.C.*, 142 F. 2d 909, 911 (C.A. 4); *Cia Mexicana De Gas* v. *F.P.C.*, 167 F. 2d 804, 806–807 (C.A. 5); *Sprague* v. *Woll*, 122 F. 2d 128, 130 (C.A. 7).

[26] In *USV Pharmaceutical Corp.* v. *Secretary of Health, Education, and Welfare*, 466 F. 2d 455 (C.A.D.C.), the order withdrawing approval of USV's bioflavonoid NDAs was reversed and the proceedings remanded, in part on the ground that the Commissioner had a burden to come forward with a statement of reasons supporting his proposed withdrawal and his notice of opportunity for hearing. In an *amicus* memorandum filed in the *Hynson* case (No. 72–394), USV contends that the issue of the burden of coming forward is not presented in *Hynson*. On the other hand, Hynson, PMA, and Squibb all rely heavily on such a contention in urging affirmance of the court of appeals' decision on the hearing issue. To the extent that Hynson, as a member of PMA, is free to assert this contention at all (see note 27, *infra*), we agree that it is properly in issue; if Hynson had the right to refuse to submit anything in response to the Commissioner's notice of opportunity for hearing, it should be no worse off simply because its submission was wholly inadequate.

Accordingly, if this Court determines that a hearing is not required in *Hynson*, and thus that the procedure followed

The industry briefs appear to take the position that FDA has the burden both to come forward with evidence showing a lack of the drug's effectiveness before it may propose to withdraw NDA approval and to prove the drug's ineffectiveness before denying a hearing on an NDA withdrawal. Neither of these positions is correct, and both positions have been specifically rejected in separate litigation brought by PMA (of which Hynson and USV are members). *Pharmaceutical Manufacturers Ass'n* v. *Richardson*, 318 F. Supp. 301, 312 (D. Del.).[27]

Under the 1962 Amendments, a drug manufacturer has the burden of showing the product's safety and effectiveness prior to marketing, and retains that burden throughout its marketing history. Sections 505 (d)(5) and 505(e)(3) of the Act both require NDA

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was lawful, FDA will provide USV another opportunity to submit data to justify a hearing, analyze any data so submitted to determine whether it indicates that adequate and well-controlled studies may exist, grant or deny a hearing in accordance with that determination, and, if it denies a hearing, publish its detailed analysis of the data in the Federal Register. If USV fails at that time to make a submission conforming to the requirements of the Commissioner's regulations, its request for a hearing will be summarily denied. The propriety of summary denial of a hearing in such circumstances was upheld in *Ciba-Geigy Corp.* v. *Richardson*, 446 F. 2d 466 (C.A. 2), which we believe adopts the correct view, and which conflicts in this regard with the opinion of the District of Columbia Circuit in the *USV* case.

[27] Since the propriety of FDA's procedures and procedural rules at issue here was adjudicated and the judicial determination was not appealed, the issues determined in the *PMA* litigation are *res judicata* as to PMA's members. See *Acree* v. *Air Line Pilots Association*, 390 F. 2d 199, 202 (C.A. 5).

disapproval or withdrawal of NDA approval not just if the drug is established by FDA to be unsafe or ineffective, but rather if at any time it is found that there is a lack of data to show safety and effectiveness. This approach places the burden of coming forward with data on the manufacturer, who is ordinarily the one who has developed the data in the first place. The statute places no different burden on FDA to disapprove the drug in the first instance than it does to withdraw approval later, since it uses the identical language in both provisions; nor does the legislative history indicate a contrary intent.

Thus, in contrast to the position taken by the industry briefs, there is no gap between the requirements for placing a drug on the market in the first instance and those for keeping it there.[28] If there is insufficient data to put the drug on the market, there would be insufficient data to keep an established drug on the market; and if new information showed that the data on which the drug was originally approved for marketing is now regarded as insufficient, the drug must be removed.

The very purpose of the 1962 Amendments requires this result, not only as to the ultimate burden of proof but also with regard to the burden of coming forward. As we have shown, Congress intended to require pre-1962 NDA'd drugs to meet the new effectiveness requirements, after a two-year moratorium during

[28] *Bell* v. *Goddard*, 366 F. 2d 177 (C.A. 7), contains an offhand statement to the contrary, but the question was not in issue in the case and was not briefed or argued to the court.

which the necessary data could be obtained.[29] The drugs had never before been reviewed and approved for effectiveness (if they had been, and the Commissioner's proposed withdrawal of approval was based on specific new evidence or analysis which had come to light, there might be a greater burden upon him to set forth this information in the notice proposing withdrawal of approval). The suggestion that the Commissioner must shoulder the burden of coming forward with a detailed review of the information in his file (and perhaps everything in the medical literature) showing that acceptable evidence of a drug's effectiveness does not exist thus ignores the concrete realities of the situation and the nature of the inquiry the statute requires him to make. It would place upon him the onerous burden of demonstrating a negative—the absence of studies—despite the fact that, if such studies do exist, information regarding them is surely in the manufacturer's files. Neither common sense nor considerations of fairness prevent placing the burden

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[29] The construction urged by the industry briefs would frustrate this intent by placing a much greater impediment to FDA's application of the Amendments to these drugs than to newly marketed therapeutic entities. The situation is virtually identical to that presented in *Environmental Defense Fund v. Finch*, 428 F. 2d 1083 (C.A.D.C.), which involved another section of the Act (relating to pesticides). The court there stated (428 F. 2d at 1092, n. 27):

"In light of Congress' strong concern about the safety of pesticide residues and the congressional intent to place the burden of persuasion on those proposing to permit a residue to remain, the fact that the present petition seeks revocation of an existing tolerance does not affect the burden of persuasion established by Congress. * * * Once new evidence bearing on the safety of pesticide residues has been adduced or cited suf-

of coming forward upon the person best situated to meet it—the manufacturer.[30]

Even if it were concluded that some basis must exist to trigger the imposition on the manufacturer of the burden of coming forward with a concrete showing that substantial evidence of effectiveness may exist, surely this requirement is satisfied by the fact that the National Academy of Sciences, drawing upon the best scientific talent available in the Nation, has concluded that the drug's effectiveness is not established.

C. THE USE OF HISTORICAL CONTROLS FOR EVALUATION OF LUTREXIN IS UNJUSTIFIED, AND THE "CONTROLS" IN HYNSON'S "STUDIES" WERE INADEQUATE ON THEIR FACE

Although Hynson argues that the testimonials presented on behalf of Lutrexin are sufficient in themselves to justify a hearing (Br. 20), ultimately its position rests upon the contention that the use of historical controls in the Gratton and Majewski studies affords sufficient grounds for a hearing (Br.

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ficient to justify reopening the issue of the validity of existing tolerances, as in the present case, the burden of establishing the safety of any tolerance remains on those who seek to permit a residue. In this connection, we note that the statute itself explicitly requires that the procedures for amending or repealing tolerances should be the same as those for establishing tolerances. 21 U.S.C. § 346a(m)."

[30] Since the NAS-NRC panels concluded that more than 13,000 of the claims they reviewed were not supported by substantial evidence (see our brief in *Bentex* at p. 18), FDA would be faced with a truly monumental task if it had to prepare a detailed substantiation of each of these conclusions before it could move against the drug. By placing the burden of coming forward on the manufacturer, the process of weeding out wholly unsubstantiated drug efficacy claims is rendered at least partially manageable.

21-24). The gist of Hynson's position is that it would be unethical to test Lutrexin against a placebo because it is "clinically-proven to be effective" (Br. 20, J.A. 37)—an assertion that assumes the answer to the very question in issue.[31]

It is well recognized that the use of so-called "historical controls," by which a patient or group of patients is compared with the generally expected clinical outcome, is almost as suspect scientifically as the use of clinical impression. Indeed, this procedure is really a simple extension of the concept of clinical impression, because it cannot eliminate the observer's or the patient's bias (*i.e.*, it is not a "blind" study), there is no randomization of subjects, and there is no pairing of controls. Of all types of scientific studies, therefore, it is the most suspect and the least reliable; it is permissible only in rare circumstances.

Professor Walter Modell, one of the nation's foremost pharmacologists, has described the fallacies of the historical control:

> It is tempting to use an easy way out, to use what has been called the historical control, i.e., a recounting of previous or personal experience or recorded experience as a basis of comparison. Often, this is not recognized as a control—and with good reason, for it is a treacherous control.

[31] Lutrexin is claimed to be effective in treatment of dysmenorrhea as well as threatened and habitual abortion. Dr. Rezek claims to have found the drug effective in his practice (J.A. 118-120). No control group was employed. The sole criterion for gauging efficacy was the subjective responses of the patients. Hynson does not contend that dsymenorrhea is either life threatening or predictable in its onset or pattern.

> No method of drug examination is more likely to lead to erroneous conclusions, because it has none of the safeguards provided by other controls, the elimination of placebo effects and of bias. It also fails utterly to provide comparable bases for examinations of control and experimental groups. Only in the case of the disease in which an irrevocable or unquestionable characteristic course has been established, and particularly when the disease is rare, is the historical control justified. [Modell & Houde, *Factors Influencing Clinical Evaluation of Drugs with Special References to the Double Blind Technique,* 167 J. Am. Med. Assn. 2190, 2194 (1958).]

For these very reasons, the FDA regulations require the use of concurrent controls on randomized patients using the double-blind technique, except in rare circumstances where to do so would be unethical. 21 C.F.R. 130.12(a)(5)(ii)(*a*)(*4*)(*iv*) (J.A. 488). Such rare circumstances include acute leukemia, poisonous snake bites, and other similar circumstances where mortality is foreordained.

The use of historical controls in evaluating Lutrexin is not justified, either ethically or scientifically.[32] In

[32] The importance of adequate scientific studies in treating threatened and habitual abortion has recently been dramatically but tragically demonstrated. It was common, during the 1950's, to treat this condition with large doses of the artificial hormone, diethylstilbestrol (DES). When controlled clinical studies failed to show the effectiveness of this drug for that use, however, its use was no longer recommended. Recently, moreover, it has been discovered that this use of DES has been associated with a very rare form of cancer of the vagina in the female offspring of mothers on whom the drug was used. Herbst et al., *Adenocarci-*

numerous other cases involving threatened and habitual abortion, studies have been undertaken with concurrent controls, using the concurrent randomized double-blind technique also required by the FDA regulations.[33] The diagnosis and clinical course of threatened and habitual abortion is highly variable, depending upon the physician, the patient and the clinical conditions.[34] Particularly because of the use of the drug during pregnancy—unquestionably the most dangerous period for drug use—it would be highly unethical

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noma of the Vagina, 284 N. Eng. J. Med. 878 (April 22, 1971); Greenwald et al., *Vaginal Cancer After Maternal Treatment with Synthetic Estrogens*, 285 N. Eng. J. Med. 390 (August 12, 1971). If it had first been required that this drug be studied under controlled clinical conditions, its use for a purpose for which it was ineffective would not have occurred, and the nation would have been spared this tragedy.

[33] Compare the detailed published plan and double-blind technique used in evaluating diethylstilbestrol for this same condition, Himsworth, *The Use of Hormones in the Management of Pregnancy in Diabetics*, 2 Lancet 833 (1955), and Dieckmann, *Does the Administration of Diethylstilbestrol during Pregnancy Have Therapeutic Value?*, 66 Am. J. Ob. Gyn. 1062 (1953), with the unplanned, uncontrolled observations of Gratton (J.A. 87–91) and Majewski (J.A. 92–117) on Lutrexin. Ten copies of the Himsworth and Dieckmann studies are being lodged with the Court for comparison purposes.

[34] For example, Dr. Gratton's "historical controls" show a live birth rate of 46 percent (J.A. 88), whereas the control group in Himsworth, *supra*, shows a fetal survival rate of 75 percent. Dr. Allen, upon whom Hynson relies, has recognized the uncertainty of ascribing benefit to a drug administered in treatment of threatened abortion: "It is, of course, difficult to prove statistically that hormone therapy does save the pregnancy as there are many pregnancies in which bleeding and cramping occur yet the pregnancy proceeds normally with no therapy other than rest in bed" (J.A. 122.).

to permit use without adequate assurance of its effectiveness. If there were adequate alternative drugs for this condition, the only ethical question would be whether Lutrexin could properly be used at all (moreover, the effective drug could properly serve as the positive control); and if there are no adequate alternative drugs, the use of a double-blind study in this situation presents no ethical issues. It is in no way comparable to the virtually certain outcome of such conditions as acute leukemia of childhood.

Even assuming, *arguendo*, that the use of proper historical controls might be justified, no attempt has in fact been made at any stage in this proceeding to justify the adequacy of the controls used by Gratton and Majewski—not even in the brief filed in this Court is it suggested that these historical controls were adequate. The regulations require, for example, that a historical control must show "the adequately documented natural history of the disease and condition in comparable patients or populations." Hynson neither documented the natural history of the disease nor demonstrated that the patients were comparable with respect to such variables as age, medical complications (*e.g.*, Rh factor, trauma, malnutrition, diabetes, and hypertension), use of alcohol and cigarettes, medical treatment during pregnancy (*e.g.*, diet, bed rest, and medication), history of previous pregnancy (*e.g.*, number, type, and history of deliveries, abortions, and miscarriages), and family obstetrical history (*e.g.*, congenital abnormalities). To this day, FDA has been provided with no information sufficient

to justify the assertion that the studies qualify as adequate and well controlled.

Finally, the use of numerous concurrent medications, the lack of a plan or protocol, the lack of any uniform criterion for patient selection, the lack of any uniform definition of "threatened abortion," and the lack of an adequate statistical analysis to show that the results were not due to chance, place these studies wholly outside the requirements of the law and the regulations. Upon close analysis of the Gratton data, it is clear that they are nothing more than a collection of case histories over a ten-year period of private medical practice, and not at all the type of scientific study contemplated by the statute and regulations. In essence, Hynson merely asserts that, at a hearing, it hopes in some way to adduce sufficient testimony to justify the scientific basis for these studies, but it has consistently declined to present any information whatever on the above points to FDA throughout these proceedings.

D. THE LACK OF HEARINGS TO DATE IS NOT SIGNIFICANT

The industry briefs note that FDA has granted no hearings since the agency instituted its summary judgment rule; they argue that this demonstrates the unfairness of the procedure.[35] There are, however, a number of reasons why no manufacturer to date has been able to demonstrate a genuine issue of fact that would justify a hearing.

FDA has implemented the 1962 Amendments by

[35] Hynson Br., No. 72-394, pp. 34-35; PMA Br. 23.

beginning with those drugs regarded as least likely to be effective or as possibly hazardous. A number of these actions have involved antibiotic combinations, which have been in substantial medical disrepute since before the 1962 Amendments, and indeed were the subject of substantial adverse comment during the hearings on those Amendments.[36] Others removed from the market have had shotgun formulas for which no scientific rationale could be imagined.[37] In general, the drugs removed thus far have been trivial at best, have had not the slightest scientific evidence to support them, and were therapeutically obsolete items that should have been discarded many years ago.[38]

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[36] *E.g., Upjohn Co.* v. *Finch*, *supra*; *Pfizer* v. *Richardson*, *supra*; *Hearings on the Drug Industry Antitrust Act before the Senate Subcommittee on Antitrust and Monopoly of the Senate Judiciary Committee*. Pt. 24, 86th Cong., 2d Sess., at 13924–13928.

[37] *E.g., American Cyanamid Co.* v. *Richardson*, 456 F. 2d 509 (C.A. 1); *Bristol Laboratories* v. *Richardson*, 456 F. 2d 563 (C.A. 1).

[38] See, *e.g.*, the detailed analyses contained in recent FDA orders denying hearings in 38 Fed. Reg. 6215–6222, 6296–6309, 6419–6422. The contention in the PMA brief (p. 23, n. 21) that FDA has in one of those orders rejected seven affidavits concluding that studies were adequate and well-controled is misleading. Affidavits were first submitted in support of the contention that adequate and well-controlled clinical studies should not be required for the drug. As an afterthought, when it became clear that such studies were required, affidavits were submitted contending that two studies which, on their face, did not meet the requirements of the statute and regulations, should nevertheless be accepted as adequate and well-controlled. 38 Fed. Reg. 6305, 6307–6308. This is thus an illustration of the industry contention that affidavits must be accepted as true, regardless of whether they are supported by the data submitted (PMA Br. 4).

Drugs on which closer issues are presented may well be forthcoming in the near future. For example, there are many "possibly effective" and "probably effective" drugs on which adequate and well-controlled clinical studies are now in progress.[39]

It is not difficult to foresee issues on which a hearing will be justified. Where FDA believes that the data are fraudulent, for example, and the company disputes that contention, a hearing would obviously be required.[40] Similarly, where the drug is admittedly effective, but there is a question of the benefit-risk ratio (*i.e.*, the drug is regarded as unsafe because its admitted effectiveness is outweighed by its lack of safety), a hearing would ordinarily be required unless there is no rational basis advanced by the manufacturer to support a contrary conclusion. Finally, where the sole issue is effectiveness, and at least two adequate and well-controlled clinical studies are submitted, a hearing might be required if FDA nevertheless rejected either or both as insufficient to demonstrate the effectiveness of the drug.[41]

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[39] Some 56 drugs that were originally classified as "probably effective" or "possibly effective" have since been reclassified as effective by FDA on the basis of new information, without the necessity for a hearing.

[40] This was the situation which resulted in the hearing held on withdrawal of the NDA approval involved in *Unimed, Inc.* v. *Richardson*, 458 F. 2d 787 (C.A.D.C.).

[41] FDA has long required more than one adequate and well-controlled clinical trial, in order to show that the results are

The cases thus far have presented none of these difficult judgmental issues. As the Sixth Circuit said in *Upjohn Co.* v. *Finch*, 422 F. 2d 944, 955, "We agree with the Commissioner that: 'No amount of examination and cross-examination can change the scientific studies and data reported into something they are not.'" When questions are presented on which examination and cross-examination can elucidate differences in judgment, however, FDA clearly anticipates holding hearings on such issues.

E. THE COMMISSIONER'S CONGRESSIONALLY ASSIGNED ROLE AS REGULATOR DOES NOT DEPRIVE HIM OF AUTHORITY TO DECIDE WHETHER A HEARING IS REQUIRED

The industry briefs raise the question whether the Commissioner of Food and Drugs may properly sit in judgment on a summary judgment motion when he is also the moving party on the issue.[42] The Act itself requires the Secretary, who has delegated his authority to the Commissioner, to determine the safety

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reproducible and not due to chance. See 21 C.F.R. 130.4(e), para. 12(c):

"* * * Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintains adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. * * *"

The material submitted by Hynson also fails on its face to satisfy this requirement, since, although there is more than one "study," there are not two by independent investigators studying the same use for the drug.

[42] Hynson Br., No. 72-394, pp. 27-30; PMA Br. 13-14.

and effectiveness of new drugs. The industry does not argue that this statutory scheme is unconstitutional, and it well settled that administrative agencies which initiate complaints may also rule upon them.[43]

The Commissioner is no more an advocate and no less an independent arbiter in ruling upon the summary judgment issue than he is in ruling upon the withdrawal issue after a full adjudicatory hearing. *Upjohn Co.* v. *Finch, supra,* 422 F. 2d at 956. The industry cites no case, nor is the government aware of one, which has held that a summary judgment motion stands on any different footing than disposition on the merits after a full hearing. Court review will in both instances reveal whether the Commissioner was arbitrary or capricious and whether there was substantial evidence of record and a basis in law to support his actions.

The Commissioner, unlike some regulatory agencies, has an affirmative duty to promote the marketing of safe and effective therapeutic agents that will help foster the nation's health, as well as the more negative duty to remove unsafe or ineffective drugs from the market. In a true sense, therefore, the Commissioner stands as an independent arbiter on issues of drug safety and effectiveness, applying the impartial and objective standards laid down by the statute and regulations, and not as an advocate for any position.

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[43] *F.T.C.* v. *Cement Institute*, 333 U.S. 683, 701–703.

III. The Scope of the Section 107(c)(4) Exemption

The industry briefs argue that, under the transition provisions contained in Section 107(c)(4) of the 1962 Amendments, only those drugs for which an NDA became effective between 1938 and 1962, and which still remain on the market at this time, are subject to the effectiveness requirements of the Amendments.[44] Some of these briefs would further narrow this coverage of the 1962 Amendments to those drugs within this class for which the manufacturer had not withdrawn the NDA, or to those which were not generally recognized as safe on the day prior to the Amendments. The industry briefs are unanimous in contending that no me-too drugs are covered by the 1962 Amendments.

The net effect of this argument would be to exempt roughly 90 percent of current prescription drugs and over 99 percent of current OTC drugs from the effectiveness requirements of the 1962 Amendments. In short, instead of making the requirement of effectiveness the rule, the industry briefs make it the rare exception. Surely, if Congress had intended this result the legislative history would reflect it.

The government's interpretation of the transition provisions, by contrast, accords to this exemption the result that one ordinarily expects from this type of statutory provision. Interpreting the term "drug" in Section 107(c)(4) to apply generically, as we suggest, would result in coverage by the 1962 Amendments of roughly 95 percent of all current prescrip-

[44] PA Br. 50–64; PMA Br. 41–54.

tion drugs and the majority but not all OTC drugs. Such prescription drugs as digitalis and quinine, and such OTC drugs as aspirin and epsom salts, would fall within the exemption, but these would be the exception rather than the rule.

IV. The Scope of the Section 201(P) Exemption

The industry briefs argue that general recognition of safety and effectiveness presents a wholly different standard from the type of evidence necessary to prove safety and effectiveness under Section 505,[45] and thus that there exists a "double standard" for drugs in the marketplace to which the effectiveness requirement applies. For some, the public can be assured of the product's safety and effectiveness. For others, the public can be assured only that there are some persons who believe them to be safe and effective, although no scientific data exist to back up that belief. The industry briefs do not propose that the products be separately labeled or identified in a way that would enable consumers to determine those which are proved to be safe and effective and those that are only believed without scientific support to be safe and effective.[46]

The implausibility of this position seems apparent on its face. Nothing in the legislative history suggests that Congress intended there to be two classes of drugs covered by the effectiveness requirements.

[45] Bentex Br. 6–7; PMA Br. 32–34.

[46] If this "double standard" in fact existed, FDA would be obligated under Sections 403(a) and 201(n) of the Act to require prominent labeling to distinguish between the two.

Indeed, Congress explicitly rejected clinical impressions and unsubstantiated opinion as a basis for determining safety and effectiveness and demanded adequate scientific proof. If this congressional judgment is to be effectuated, it is clear that there can be no general recognition of safety and effectiveness within the meaning of the Act without adequate scientific evidence to support it.[47]

CONCLUSION

For the foregoing reasons, the judgments in *Bentex* and *Hynson* should be reversed, the judgment in *CIBA* should be affirmed, and the judgment in *USV* should be affirmed on the grounds specified in the government's brief.

Respectfully submitted.

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APRIL 1973.

[47] See, for example, the definitions of "safety" and "effectiveness" promulgated by FDA for OTC drugs, 37 Fed. Reg. 9464, 9474, which require adequate scientific evidence before general recognition of safety or effectiveness may occur.

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IN THE

Supreme Court of the United States

OCTOBER TERM, 1972

No. 72-666

USV PHARMACEUTICAL CORPORATION, PETITIONER

v.

CASPAR W. WEINBERGER, SECRETARY OF HEALTH, EDUCATION AND WELFARE, AND CHARLES C. EDWARDS, COMMISSIONER OF FOOD AND DRUGS

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit

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REPLY BRIEF FOR PETITIONER

When the Drug Amendments of 1962 were enacted into law, the Food and Drug Administration publicly endorsed the interpretation of the "grandfather clause" here urged by petitioner (see Pet. Br. 4a-5a). Subsequently-realized dissatisfaction with the statute, we demonstrated in our principal brief, is the crux of the government's present position; a rewriting of the 1962 legislation to enlarge its coverage beyond that provided by Congress is what the government seeks from this Court. The new arguments pressed in the government's responding brief merely confirm that conclusion.

A. NOTHING IN THE NEW RATIONALE ADVANCED BY THE GOVERNMENT REFUTES THE RULING OF THE COURT OF APPEALS THAT "GRANDFATHERED" STATUS IS CONFERRED UPON "ME-TOO" PRODUCTS BY THE LITERAL TERMS OF THE STATUTE.

The issue as to the status of pre-1962 "me-too" products under Section 107(c)(4) is whether, in 1962, such a product was "covered by an effective [new drug] application under section 505 * * *" (Section 107(c)(4)(C)).

No longer does the government maintain, as it did in responding to the petition for certiorari,[1] that there were "generic attributes" of a new drug application for a particular product which "covered" all "me-too" products similar in composition and use. Now, the government "agree[s] that an application under Section 505 is and always has been personal to the manufacturer who files it and particular to the product or products it names" (Resp. Br. 47).

It is similarly now conceded by the government that, contrary to the apparent thrust of its original memorandum in this Court,[2] and as petitioner therefore undertook to show (Pet. Br. 39-45), the legal basis for marketing a "me-too" without filing an NDA was *not* the existence of an effective NDA held by a pioneer manufacturer, but subsequent general recognition of the product's safety, taking the product out of the statutory definition of "new drug". Thus, as correctly described by the government, after the NDA for a pioneer product had become effective, and "after the drug was on the market for a time, it would acquire the necessary general recognition and use to enable it to escape from the 'new drug' category" so that "thereafter, anyone could market a me-too copy free of administrative

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[1] Resp. Mem., pp. 10-11.

[2] *Ibid.*

premarketing regulation" (Resp. Br. 45-46).[3] And whether an NDA'd product subsequently became generally recognized as safe depended on the particular facts; some did, while many did not, thus "escape from the 'new drug' category" so as to allow the appearance of "me-too's" (see pp. 17-18 *infra*).

Although the government has abandoned the grounds on which it previously challenged the court of appeals' ruling that "me-too" products were "not covered by an effective application under section 505", and thus "[meet] literally the criteria for exemption stated in the 'grandfather clause'" (A. 470), its counsel now press a new rationale for its position. *Cf. Investment Co. Institute* v. *Camp*, 401 U.S. 617, 627-28 (1971). Noting that the role of Section 107(c)(4) is to determine the applicability of the amended definition of "new drug" in Section 201(p) of the Act, and that Section 201(p) defines "new drug" in terms of classes rather than particular products, government counsel urge that Section 107(c)(4) must also be applied to drugs by classes, so that if any product in a given class is ineligible for "grandfathered" status then every product in the class is likewise ineligible (Resp. Br. 43-44).

1. What this argument overlooks is that, in delineating the reach of the amended Section 201(p) definition, Congress established a standard drawn from *Section 505, which, as the government now concedes, is purely personal and particularized in its impact.* If Congress had not included Clause (C) in Section 107(c)(4), and if "grandfathered" status had thus been conferred upon "any drug" on the market in 1962 which was not then a "new drug" under the existing Section 201(p) definition, the government could

[3] The government thus confirms the lack of merit in the repeated assertions of *amici* American Public Health Association *et al.* (APHA Br. 34-35; *id.* at 13, 17), that "me-too" products were "obviously" marketed on the authority of effective NDA's for pioneer products.

plausibly treat Section 107(c)(4) as "generic" in its impact. But in listing the criteria for "grandfathered" status under the 1962 amendments to the Section 201(p) definition, Congress went beyond mere reference to the date the product was first marketed and to its "generic" regulatory status under the existing definition of "new drug". By adding as a third criterion the regulatory status of the product under Section 505, *i.e.*, whether the product was "covered by an effective application under section 505", Congress made "grandfathered" status turn upon the regulatory status of the precise product, as made by its particular manufacturer, rather than of its generic class.

The justification now asserted by the government for denying "grandfathered" status to an entire generic class of products, merely because some products in the class are ineligible, disregards the critical relationship of Section 505 to Clause (C) of Section 107(c)(4). The definition of "new drug" prescribed in Section 201(p) may indeed be applicable according to generic class, but Congress, by including the Section 505-based Clause (C) among the criteria for exemption from the amendment to that definition, conferred the exemption on a product-by-product basis. Under Section 505, the coverage of a new drug application is not generic but personal to the particular manufacturer and product named therein; hence Clause (C) is similarly personal and particularized.

2. Nor is the government's argument for "genericity" aided by its reliance upon differences in wording between Clause (C) of Section 107(c)(4) and other, concededly personal and particularized, provisions of the statute. There is nothing "more particularized" (Resp. Br. 44) in the language of Section 505(a) prohibiting shipment of "any new drug, unless an application * * * is effective with respect to such drug", or in the reference in Section 107(c)(3) to "any drug with respect to which an appli-

cation * * * is deemed to be an approved application", than in the language of Section 107(c)(4)(C) conferring "grandfathered" status on "any drug which * * * was not covered by an effective application * * *."

Indeed, the same words in Section 505(a) now characterized as "personal" were argued by the government, in responding to the petition for certiorari, to have "suggested a broader, generic coverage for NDA's" (Resp. Mem., p. 10). The semantic distinction now relied upon is thus plainly without substantive significance.

All these modes of expression, however, are "more particularized" than Section 201(p), which has always classified a drug as "new" on the basis of whether it is a drug "the composition of which is such that such drug is not generally recognized * * * as safe * * *." The phrase which makes Section 201(p) generic in its operation is not the phrase "any drug", but the phrase "the composition of which is such".

Moreover, contrary to the government's suggestion (Resp. Br. 44), the assertedly generic words "covered by" do in fact appear in the statutory provisions now sought to be contrasted with Clause (C) of Section 107(c)(4). The temporary moratoria imposed by Section 107(c)(3), which postponed the applicability of enumerated provisions of the 1962 amendments as to products "with respect to which an application * * * is deemed to be an approved application", were operative only so long as such products were "intended solely for use under conditions prescribed * * * in labeling *covered by such approved application*" (emphasis added). This use of both the "covered by" and the "with respect to which" modes of expression in the concededly personal and particularized Section 107(c)(3) demonstrates, we submit, that the significance which the government would now attribute to these differences in language could not have been intended by Congress.

3. Although it no longer argues that pre-1962 "me-too" products were marketed on the legal authority of NDA's which had previously been filed and which FDA had allowed to become effective for similar products, the government nevertheless suggests (Resp. Br. 45-47) that in some ultimate sense the marketing of "me-too" products "hinged on" the pioneer NDA's. According to this vestigial remnant of the government's original argument, there could have been no general recognition of safety (now conceded by the government to be the legal basis for marketing the "me-too's") were it not for widespread use of the drug; there could not have been widespread use were it not for the marketing of the pioneer product; and there could have been no marketing of the pioneer product were it not for the NDA covering that product.

Such fine-spun logic is far too strained, we submit, to provide a basis for refusing to give the language of Section 107(c)(4) its literal and obvious significance.[4] There is certainly no evidence that Congress ever contemplated such an extended view of the reach of "an effective application under section 505", whose personal and particularized nature (as spelled out in our principal brief, Pet. Br. 27-36, and now conceded by the government) had been explicitly and accurately described by Secretary Ribicoff in the course of the legislative hearings (see Pet. Br. 45-47).

To the contrary, as we have shown (Pet. Br. 47-51), Congress affirmatively demonstrated elsewhere in the 1962 amendments that it fully understood the personal and particularized nature of an "effective application under section 505". And if, as the government suggests (Resp. Br. 29), Congress was unaware in 1962 that many pharmaceutical products then on the market, being "me-too's" generally recognized as safe from the outset, were neither

[4] *Cf. Wong Sun* v. *United States*, 371 U.S. 471, 487 (1963).

"new drugs" nor "covered by an effective application under section 505", then plainly there is no basis for any speculation that its reference to the well-understood Section 505 application incorporated the remote theorizing now traced by government counsel to justify the untenable position that the coverage of a Section 505 NDA is generic.

B. THE GOVERNMENT'S BELATED SUGGESTION OF UNCONSTITUTIONALITY IN THE COURT OF APPEALS' INTERPRETATION OF THE "GRANDFATHER" CLAUSE IS FRIVOLOUS.

In support of its suggestion that the Constitution might bar Congress from conferring "grandfathered" status on "me-too" products (Resp. Br. 35), if the amended definition of "new drug" were made applicable to comparable products then being marketed under effective NDA's, the government invokes three decisions of this Court overturning State regulatory legislation under the Equal Protection Clause of the Fourteenth Amendment. The "continuing validity" of one of these [5] was expressly called into question by the Court in *United States* v. *Maryland Savings-Share Ins. Corp.*, 400 U.S. 4, 7 n.2 (1970), where a district court judgment holding unconstitutional a "grandfather" provision in the Internal Revenue Code was summarily reversed. And of course the Equal Protection Clause has no application to Congress, which is bound only to avoid classifications "so irrational as to violate the Due Process Clause of the Fifth Amendment" (*Hurtado* v. *United States*, No. 71-6742, decided March 5, 1973, slip op., p. 12).

Contrary to the government's assertion, differences in the "marketing and regulatory history of each individual product" (Resp. Br. 32) plainly meet the test of "ra-

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[5] *Mayflower Farms, Inc.* v. *Ten Eyck*, 297 U.S. 266 (1936), cited at p. 35 of the government's brief.

tional justification'' (*United States* v. *Kras*, No. 71-749, decided January 10, 1973, slip op., p. 13) applicable to classifications under economic and social welfare statutes such as the Federal Food, Drug, and Cosmetic Act. It was entirely reasonable for Congress, by including Clause (C) in Section 107(c)(4), to continue in force, as to each individual product, the administratively or judicially enforced regulatory scheme applicable to it, as the case might be, when the administrative scheme was expanded in content and coverage. Under the court of appeals' construction of Section 107(c)(4) as to ''me-too'' products, individual products subject to the administrative ''new drug'' regulatory procedure in 1962 continue to be so regulated, while products not then being regulated administratively as ''new drugs'' continue to be regulated under the judicially enforced regulatory scheme applicable to all other drugs.[6] Such is the thrust of every ''grandfather'' clause, including the one upheld in *United States* v. *Maryland Savings-Share Ins. Corp., supra.*[7]

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[6] Even assuming that the Constitution required Congress to impose some form of regulation on efficacy claims for ''me-too'' and formerly NDA'd products if it imposed such regulation on products still covered in 1962 by effective NDA's, that duty was plainly met by the continuation in force of the judicially-applied prohibition against misbranding (see Pet. Br. 64-65 & n.151), whether or not the government now finds enforcement of the misbranding prohibition impractical (Resp. Br. 35-36). See *United States* v. *Kras, supra*, slip op., p. 12.

[7] Yet another ''rational justification'' which may be perceived for Section 107(c)(4), as thus interpreted, is Congress' expressed desire to avoid interfering with FDA's capacity to deal both fairly and expeditiously with the products within its jurisdiction (S. Rep. No. 1744 (pt. 1), 87th Cong., 2d Sess. 17). See *United States* v. *Maryland Savings-Share Ins. Corp., supra*, 400 U.S. at 6-7. According to the government (Brief for Petitioners, pp. 19, 30, 35, *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, No. 72-394), the feared overload would indeed result if the statute were construed to subject pre-1962 ''me-too's'', which are generally recognized as safe, to new drug regulation by the agency.

Nor would Section 107(c)(4) as applied to "me-too's" by the court of appeals be incapable of "rational justification" under the Due Process Clause merely because, as the government appears to argue, the Section 201(p) amendment would thereby not extend to all manifestations of the problem to which the amendment was assertedly addressed. The Equal Protection Clause does not require States to legislate either against all instances of an alleged evil or against none, whether the partial regulation is intentional or the result of limited legislative perception. *McDonald* v. *Board of Election Commissioners*, 394 U.S. 802, 809, 811 (1969). By the same token, no objection could be raised under the Fifth Amendment against an asserted failure of Congress to legislate comprehensively on the subject of pharmaceutical regulation. *Richardson* v. *Belcher*, 404 U.S. 78, 81 (1971); *United States* v. *Carolene Prods. Co.*, 304 U.S. 144, 151 (1938).[8]

[8] The government makes no effort to address the true Fifth Amendment issues raised by its position in this case, which are (a) whether Section 505(a) would give sufficiently clear notice if construed to make it a criminal offense for a "me-too" manufacturer to market his product after approval of the pioneer NDA is revoked (Pet. Br. 31-32), and (b) whether Section 505(e) contains sufficient provision for notice and an opportunity for hearing to "me-too" manufacturers so as to bind them in Section 505(e) revocation proceedings against the pioneer manufacturers (Pet. Br. 29-31). Indeed, the constitutional difficulties in the government's position are only compounded by its assertions with respect to pre-1962 products which came on the market as "old drugs" prior to the time any NDA became effective for any "similar" or "related" product (even under the government's comprehensive definition of those terms). According to the government (Resp. Br. 46 n.29), the subsequent action of some other manufacturer in filing an NDA, and in having it become effective for his own product, resulted in the original never-NDA'd product being "covered by" the subsequent NDA for purposes of Section 107(c)(4). Thus, the government suggests, when the Section 201(p) definition was amended in 1962 it became a criminal offense to market the original product without at least an abbreviated NDA, even though the

C. THE SCOPE ATTRIBUTED BY THE GOVERNMENT TO SECTION 107(c)(4), TO AVOID MAKING SURPLUSAGE OF THE ENTIRE PROVISION, IS FORECLOSED BY FDA'S PAST INTERPRETATION OF THE "NEW DRUG" DEFINITION.

1. In its anxiety to escape the conclusion (Pet. Br. 60-63) that its construction of Section 107 (c)(4) would leave that provision meaningless and redundant in light of the original "grandfather" provision in Section 201(p) of the 1938 Act, the government overlooks a fundamental principle on which FDA has premised its enforcement of the "new drug" preclearance requirement ever since 1938. The government now asserts (Resp. Br. 17, 51) that post-1938 never-NDA'd proprietary products lacking a history of use for the particular purpose claimed, or in the particular combination employed, were not "new drugs" prior to 1962, and thus now qualify for "grandfathered" status under Section 107(c)(4). Contrary to this suggestion, however, FDA has always interpreted the definition of "new drug" in Section 201(p) to comprehend all drugs, whether prescription or proprietary, which "consisted of a new combination of ingredients or * * * [which] advanced new claims" (Resp. Br. 17), even those consisting solely of "old, established ingredients that had long been generally recognized as safe" (*ibid.*) in other combinations, or for other uses, in the same dosage.

This is clear from the interpretive regulations promulgated under Section 201(p) contemporaneously with the enactment of the original statute (3 Fed. Reg. 1847), and still in force (21 C.F.R. § 130.1(h)), which provide that:

> "The newness of a drug may arise by reason (among other reasons) of:
> * * *

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original manufacturer had no notice of the NDA in question (Pet. Br. 28 n.43). It is plainly the government's interpretation of the statute, not petitioner's or the court of appeals', which opens up the due-process thicket.

(2) The *newness* for a drug use *of a combination* of two or more substances, none of which is a new drug. * * *

(4) The *newness of use* of such drug *in* * * * *a disease,* * * * even though such drug is not a new drug when used in another disease * * *.

(5) The *newness of a* * * * *condition of use* * * * *in the labeling* of such drug, even though such drug when used in * * * different condition, is not a new drug." (Emphasis added.)

The underlying principle, as explained in one of the earliest informal opinions published by FDA, was that "the statute in defining a new drug deals with both the product and the labeling."[9] The general recognition of safety ("GRAS") which has always been deemed necessary to keep a product out of the "new drug" category is GRAS *for the particular claim in question,* not recognition of safety in the abstract, or in use for some other purpose. *Merritt Corp.* v. *Folsom,* 165 F. Supp. 418 (D.D.C. 1958).[10] And, importantly, FDA has always contended that a consensus of expert opinion on that precise issue must exist in fact, so that, absent a history of actual use for the purpose claimed, there could be no general recognition of safety for that use.

Thus, enforcement actions under Section 505(a) both prior to 1962 and thereafter[11] have been brought against

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[9] TC-78 (undated), in KLEINFELD & DUNN, FEDERAL FOOD, DRUG, AND COSMETIC ACT 1938-1949 602. The immediately preceding opinion, TC-77, was dated February 19, 1940, and the opinion next following, TC-79, was dated February 21, 1940.

[10] *Merritt* involved neomycin sulfate, which was generally recognized after 1955 as safe for the uses theretofore claimed for that drug. The district court held that the product was still a "new drug" when recommended for acne, however, because of a lack of general recognition that the drug was safe for that "particular disease". 165 F. Supp. at 421.

[11] As we noted in our principal brief (Pet. Br. 61 n.142), the standard of "general recognition" established in Section 201(p) and spelled out in FDA regulations (p. 11 *supra*) dates from 1938 and was not amended or even considered in 1962. See note 16 *infra.*

proprietary as well as prescription products on the premise that absence of a history of use for the particular purpose claimed,[12] or in the particular combination of ingredients employed,[13] is sufficient to confer "new drug" status upon the product in question. Indeed, elsewhere in the consolidated cases before this Court the government asserts that, even with a history of use, "lack of documented sources of information bars the widespread expert knowledge of the drug's effectiveness *or safety* necessary to achieve exemption from Section 505."[14] The government's contention to the contrary in the instant case is at war with these long-standing administrative regulations and enforcement policies.

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[12] *United States* v. *354 Cartons* • • • *Trim Reducing-Aid Cigarettes*, 178 F. Supp. 847 (D.N.J. 1959) (tartaric acid as appetite depressant); *United States* v. *42 Jars* • • • *"Bee Royale Capsules"*, 264 F.2d 666 (3d Cir. 1959) (queen-bee jelly as aphrodisiac and hair restorer); *United States* v. *Articles of Drug* • • • *"Quick-O-Ver"*, 274 F. Supp. 443 (D. Md. 1967) (combinations including ephedrine and phenaticin, two ingredients GRAS for over-the-counter sale when appropriately labeled, sold for relief of hangovers in which user "would not be disposed or able to read the warnings"); *United States* v. *Article* • • • *Sudden Change*, 409 F.2d 734 (2d Cir. 1969), *United States* v. *Article* • • • *"Line Away Temporary Wrinkle Smoother, Coty"*, 415 F.2d 369 (3d Cir. 1969), and *United States* v. *Article* • • • *"Helene Curtis Magic Secret"*, 331 F. Supp. 912 (D. Md. 1971) (all involving cow's blood albumen as topically-applied temporary wrinkle smoother).

[13] *United States* v. *Article of Drug* • • • *"Furestrol* • • •", 294 F. Supp. 1307 (N.D. Ga. 1968), *aff'd per curiam*, 415 F.2d 390 (5th Cir. 1969) (new combination of GRAS prescription ingredients); *United States* v. *An Article of Drug* • • • *Excedrin P.M.*, CCH Food Drug Cosm. L. Rep. ¶ 40,486 (E.D.N.Y. 1971) (new combination of GRAS over-the-counter analgesics and antihistamine); see *Smith Kline & French Labs.* v. *Richardson*, Civ. No. 71-387, E.D. Pa., decided February 26, 1971, *appeal dismissed*, No. 71-1484, 3d Cir. 1972 (same, plus caffeine).

[14] Brief for Respondents, p. 23 n.18, *Hynson, Westcott & Dunning, Inc.* v. *Weinberger*, No. 72-414 (emphasis added).

2. The legislative history of the 1962 amendments clearly discloses, moreover, that Congress assumed the existing law to be as FDA had traditionally construed it. In its initial report on S. 1552, which struck out as unnecessary the provision amending the definition of "new drug", the Senate Judiciary Committee stressed that under existing law any drug was "new"

> "if it is not generally recognized by qualified experts as 'safe for use under the conditions' claimed or has not (otherwise than in research) been used to a material extent or for a material time under such conditions." [15]

Whether or not this understanding was accurate, insofar as the pre-1962 "new drug" status of new claims for or combinations of familiar over-the-counter ingredients was concerned, it was in fact the understanding on which Congress acted when Section 107(c)(4) was added to the 1962 legislation in consequence of the ultimate decision to amend the "new drug" definition in Section 201(p).[16] Congress therefore could not have expected Section 107(c)(4) to protect these proprietary products except to the extent that, as might have been the case with any pre-1962 product whether proprietary or prescription, they were neither

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[15] S. Rep. No. 1744 (pt. 1), 87th Cong., 2d Sess. 17. This was spelled out even more explicitly in the separate statement of Senators Dirksen and Hruska, who repeatedly referred to the phrase "under the conditions prescribed" in § 201(p), and concluded that these words "are interpreted, and can only be interpreted, to mean that it is the use claimed for a drug that determines whether or not it is a new drug * * *" (*id.* at 59).

[16] This understanding could in no event have effected any change in the construction thereafter to be placed upon the general-recognition standard of § 201(p), however, inasmuch as that aspect of the provision was neither amended nor even technically re-enacted by the 1962 amendments. The amendments merely added the phrase "and effective" or the phrase "and effectiveness" to the existing § 201(p) where appropriate (Drug Amendments of 1962, § 102(a), 76 Stat. 781).

"new drugs" in 1962 nor then "covered by an effective application under section 505". The government's effort to conjure up some special significance for these products under Section 107(c)(4), so as to justify excluding "me-too" products from "grandfathered" status, must accordingly fail.

3. Nor is the government helped by Senator Kefauver's reference to "proprietaries now on the market", on which it principally relies (Resp. Br. 28, 52).[17] As the government recognizes (Resp. Br. 28 n.16), this statement reflected a belief that *no* proprietary product was covered by an effective NDA, although in fact the contrary was frequently true. It is apparent that the Senator mistakenly equated "ethical drug" or "prescription drug" with "NDA'd drug", and "proprietary drug" or "over-the-counter drug" with "drug not covered by an effective NDA".

This same confusion was reflected elsewhere in the floor speech quoted by the government. Earlier in his remarks, Senator Kefauver characterized it as "difficult to arbitrarily make a distinction * * * between proprietary drugs and ethical drugs" (108 Cong. Rec. 17368). The reason for this difficulty, he explained, was that "some ethical drugs become proprietary drugs" (*ibid.*).

Given the Senator's belief that "ethical" drugs were those covered by effective NDA's and that "proprietary" drugs were those not covered, it is evident that his subsequent reference to "proprietaries now on the market" as being exempted from the effectiveness provisions of

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[17] Whatever may have been implied in the separate statement of views by Senators Dirksen and Hruska, which the government also cites (Resp. Br. 52 n.36), it is noteworthy that those two Senators' as the principal opponents of Senator Kefauver's proposed amendment of the "new drug" definition, may well have been inclined to overstate its reach by understating the reach of the principle which even they recognized was embedded in existing law (*cf. Nat'l Woodwork Mfrs. Ass'n* v. *NLRB*, 386 U.S. 612, 639-40 (1967)).

the amendments does not refute, but corroborates, the conclusion of the court of appeals in the instant case. "Me-too" products, because they had come on the market without effective NDA's after a pioneer product had become generally recognized as safe, *i.e.*, had "become proprietary drugs", are encompassed by the "grandfather" provisions of Section 107(c)(4).

D. NO EVIDENCE CAN BE FOUND IN EITHER THE STATUTE OR ITS LEGISLATIVE HISTORY FOR THE GOVERNMENT'S ASSERTION THAT CONGRESS INTENDED TO APPLY THE AMENDED REGULATORY SCHEME PRESCRIBED FOR "NEW DRUGS" TO VIRTUALLY EVERY PRODUCT ALREADY ON THE MARKET IN 1962.

1. As the government recognizes (Resp. Br. 24), only a "limited expression of purpose" can be found in the legislative history of the amendment to the definition of "new drug" in Section 201(p). That purpose was "to eliminate any possible ambiguity" that a new claim for an existing product, or for a future product approved as to other claims, would require premarketing clearance by FDA (see Pet. Br. 53-55). The government's attempt to impute a broader, unexpressed, purpose to Congress in amending Section 201(p) (Resp. Br. 24-36) rests entirely upon Congress' inclusion of the transitional provisions whose intended meaning is sought to be illuminated by reference to the purpose in question. This is bootstrap logic, nothing more.

Nor do these transitional provisions, even on their own footing, support the inference urged by the government as to the purpose of the amendment to Section 201(p). Paragraph 2 of Section 107(c) says nothing about the applicability of that amendment (or of any other provision of the new law) to existing products, but merely converts "effective" NDA's into "approved" NDA's in conformity with the new terminology. The two-year pro-

vision in Paragraph 3 of Section 107(c) does not deal with products which, like "me-too's", were then outside the scope of the administratively-applied regulatory scheme governing "new drugs", but only with products already subject to that regulatory scheme, and thus sheds no light on whether Congress intended in amending Section 201(p) to impose the "new drug" scheme on existing products not already embraced within it.

The evidence of Congress' intent in that regard is supplied, we submit, (1) by the "limited expression of purpose" actually provided by the Senate Judiciary Committee in justification of the Section 201(p) amendment, and (2) by the refusal of both the Senate and the House to rest with the Administration's proposed "grandfather" language (see Pet. Br. 56-59). The government seemingly suggests that, in adding Section 107(c)(4) to the bill, Congress merely supplied the "reasonable transition provision" which the Administration had indicated would be acceptable if the "new drug" regulatory scheme were extended to existing products (Resp. Br. 27 n.14). But such a transition provision was already contained in Section 108(c) of H.R. 11581, the Administration's bill in the House, and in Amendment No. 4(g)(2) in the Administration package sent up to the Senate.

As the government recognizes, Section 107(c)(4) was enacted *in addition to* the equivalent of the Administration's proposed transition provision. The inference is inescapable that, despite the Administration's urging, Congress did *not* wish to extend the "new drug" regulatory scheme to existing products then being marketed outside that scheme, so long as no new claims for the products were made, and that Section 107(c)(4) was added to the language proposed by the Administration precisely to avoid this unwanted result.

2. The government's contention that to recognize the "grandfathered" status of "me-too's" would exempt a

greater number of pre-1962 products from "new drug" regulation than would be covered (Resp. Br. 33-34) is both factually unfounded and legally of no consequence. Although according to the government some 9,500 NDA's and 12,000 supplemental NDA's became effective between 1938 and 1962,[18] it is undisputed that not more than 1,000 of the products covered arguably became generally recognized as safe and thus no longer "new" prior to 1962, so as to permit the marketing of non-NDA'd "me-too" versions by other manufacturers.[19] Moreover, the affidavit lodged with this Court by the Pharmaceutical Manufacturers Association as *amicus curiae* suggests that more than 75% of the pre-1962 products alleged to be ineffective by FDA have already been voluntarily removed from the market,[20] so that the regulatory significance of allowing pre-1962 non-NDA'd products to continue on the market without proving efficacy in an administrative proceeding would appear to be limited.[21] And, as the government rec-

[18] Brief for Petitioners, p. 7, *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, No. 72-555.

[19] *Hearings on Drug Efficacy Before a Subcommittee of the House Committee on Government Operations*, 91st Cong., 1st Sess. 375 (testimony of HEW Ass't Gen. Counsel Goodrich).

[20] PMA Br. 26 n.27.

[21] It is not an issue in this case whether (as alleged by FDA) substantial evidence is in fact lacking that petitioner's pre-1962 citrus flavonoid products are effective for their recommended uses, which the district court found after trial to be solely the control of abnormal capillary permeability and fragility (A. 465). The government's assertion here that the products are also recommended to correct the underlying ailments described in the labeling in which this symptom may occur (Resp. Br. 7) is inexplicable, in view of (a) the district court's direct and emphatic rejection of that argument (A. 450-51); (b) the court of appeals' failure to disturb the finding when urged by the government to overturn it; and (c) the government's representation to this Court in responding to the petition for certiorari (Resp. Mem., p. 6 n.9) that "after a full district court trial, there are now no disputed issues of fact in the present case, * * *."

ognizes (Resp. Br. 51 n.34), the Section 107(c)(4) exemption does not bar removal of such products from the market for inefficacy, requiring only that such removal be through a misbranding action rather than pursuant to "new drug" regulation.

But even if Congress in 1962 had misapprehended the relative breadth of the Section 201(p) amendment as applied to existing products, compared with the exemption from that amendment provided for such products in Section 107(c)(4), the government would not be justified in asking this Court to refuse to implement the exemption in accordance with its terms. The question is what Congress intended, not what Congress would have intended had it perceived the facts differently. As noted in our principal brief (Pet. Br. 67-68), the Court has consistently declined the government's occasional invitation "to engraft on a statute additions which we think the legislature logically might or should have made" (*United States* v. *Cooper Corp.*, 312 U.S. 600, 605 (1941)). Yet such an invitation, we have demonstrated, is the sum and substance of the government's case for excluding petitioner's pre-1962 products from the scope of the "grandfather" clause.

CONCLUSION

Shifting its position from that taken in response to the petition for certiorari, the government has advanced an entirely new rationale for avoiding, as to never-NDA'd "me-too" products, the interpretation of Section 107(c)(4) which the court of appeals deemed to be required by the explicit terms of the statute. For the reasons stated herein, the new arguments are as devoid of merit as those previously pressed by the government and discussed in our principal brief. The government concedes, however (Resp. Br. 13), that the court of appeals erred in failing to accord petitioner's never-NDA'd "me-too" products the same treatment under Section 107(c)(4) to which identical never-

NDA'd products of other manufacturers are entitled. Therefore, as requested in our principal brief, the judgment below should be reversed.

Respectfully submitted,

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April 13, 1973

NOTE: Where it is feasible, a syllabus (headnote) will be released, as is being done in connection with this case, at the time the opinion is issued. The syllabus constitutes no part of the opinion of the Court but has been prepared by the Reporter of Decisions for the convenience of the reader. See *United States* v. *Detroit Lumber Co.*, 200 U.S. 321, 337.

SUPREME COURT OF THE UNITED STATES

Syllabus

WEINBERGER ET AL. *v.* HYNSON, WESTCOTT & DUNNING, INC.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 72-394. Argued April 17, 1973—Decided June 18, 1973*

The Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1962, establishes a system of premarketing clearance for drugs and prohibits in § 505 (a) the introduction into commerce of any "new drug" unless a new drug application (NDA) filed with the Food and Drug Administration (FDA) was *effective* with respect to such drug. Under the Act procedures were established for filing "new drug" applications not only for the *safety* of drugs but for their *efficacy* as well. Standards were provided under which, after notice and hearing, FDA could refuse to allow an NDA to become effective, or could suspend an NDA in effect on the basis of new evidence that the drug was not effective. FDA is directed to refuse approval of an NDA and to withdraw prior approval if "substantial evidence" (§ 505 (d)) that the drug is effective for its intended use is lacking. All NDA's "effective" prior to 1962 were deemed "approved" and manufacturers were given two years to develop substantial evidence of effectiveness during which previously approved NDA's could not be withdrawn by FDA for the drug's lack of effectiveness. The 1962 Act also contained a "grandfather" clause exempting from the effectiveness requirements any drug which on the day preceding enactment (1) was commercially used or sold in the United States, (2) was not a "new drug" as defined in the 1938 Act, and (3) "was not covered by an effective application" for a new drug under the 1938 Act. The FDA had permitted more than 9,000 NDA's to become effective between 1938 and 1962, of which some 4,000 were still on the market. Additionally, manufacturers have marketed thousands of

*Together with No. 72-414, *Hynson, Westcott & Dunning, Inc.* v. *Weinberger et al.*, also on certiorari to the same court.

Syllabus

"me-too" drugs without applying for clearance, drugs similar or identical to drugs with effective NDA's, marketed in reliance on the "pioneer" drug application approved by the FDA. To aid it in fulfilling the statutory mandate to review all marketed drugs, whether or not previously approved, for their efficacy, the FDA retained the National Academy of Sciences-National Research Council (NAS–NRC) to create expert panels to review by class the efficacy of each approved drug. Holders of NDA's were invited to furnish the panels with the best available data to establish efficacy and the FDA announced that it would apply NAS–NRC efficacy findings to all drugs, including the "me-too" drugs. Respondent in No. 72–394 (Hynson) had filed an application for a drug called Lutrexin under the 1938 Act. The FDA informed Hynson that the studies submitted with the application were not sufficiently well controlled to justify the claims of effectiveness, but allowed the application to become effective since the 1938 Act permitted evaluation of a new drug solely on the basis of its safety. When the 1962 amendments became effective Hynson submitted evidence of the efficacy of the drug, but the NAS–NRC panel reported that Hynson had not satisfied the requirements. Notice of an intention to withdraw approval of the NDA's covering the drug was given. Before the hearing, Hynson brought suit in the District Court for a declaratory judgment that the drug was exempt from the *efficacy* review provisions of the 1962 Act, or that there was no lack of substantial evidence of the drug's efficacy. Petitioners' motion to dismiss was granted. The Court of Appeals reversed, holding that while the drug was not exempt, Hynson was entitled to a hearing on the substantial evidence issue. No. 72–414 is a cross-petition by Hynson from the judgment of the Court of Appeals, which suggested that only a district court has authority to determine whether Lutrexin is a "new drug." While Hynson agrees that the Commissioner has authority to determine new drug status in proceedings to withdraw approval of the product's NDA, some manufacturers, parties to other suits in this group of cases, advance the contrary view. *Held:*

1. The 1962 Amendments and the regulations issued thereunder, which express well-established principles of scientific investigation, in their reduction of the "substantial evidence" standard to detailed guidelines for the protection of the public, make the FDA's so-called administrative summary judgment procedure appropriate. Pp. 5–9.

Syllabus

2. FDA's procedure, whereby it will not provide a formal hearing when it is apparent at the threshold that the applicant has not tendered *any* evidence which *on its face* meets the statutory standards as particularized by the regulations, is valid. *United States* v. *Storer Broadcasting Co.*, 351 U. S. 192, *FPC* v. *Texaco*, 377 U. S. 33. Pp. 9–11.

3. In No. 72–394, the Court of Appeals' holding that Hynson was entitled to a hearing on whether its submission of evidence satisfied its threshold burden of providing "substantial evidence" is affirmed. Pp. 11–12.

4. The heart of the statutory procedure is the grant of primary jurisdiction to the FDA, subject to judicial review when administrative remedies are exhausted. Pp. 12–17.

5. Although a drug can be "generally recognized" by experts as effective for intended use within the meaning of the Act only when that expert consensus is founded upon "substantial evidence," any ruling on Lutrexin's "new drug" status is premature, and must await the outcome of the hearing on whether Hynson submitted "substantial evidence," as held in No. 72–394 (item 3, *supra*). Pp. 17–21.

6. Lutrexin is not exempt under the "grandfather" provisions of the 1962 Act, as held by the FDA and the Court of Appeals, and their construction accords with the legislative history which suggests that the exemption is afforded only for drugs that never had been subject to new drug regulation. Pp. 21–23.

461 F. 2d 215, affirmed as modified.

DOUGLAS, J., delivered the opinion of the Court, in which BURGER, C. J., and WHITE, MARSHALL, BLACKMUN, and REHNQUIST, JJ., joined. POWELL, J., filed an opinion concurring in the result as to Part I and joining in Part II of the Court's opinion. BRENNAN, J., took no part in the consideration or decision of the case. STEWART, J., took no part in the decision of the case.

NOTICE: This opinion is subject to formal revision before publication in the preliminary print of the United States Reports. Readers are requested to notify the Reporter of Decisions, Supreme Court of the United States, Washington, D.C. 20543, of any typographical or other formal errors, in order that corrections may be made before the preliminary print goes to press.

SUPREME COURT OF THE UNITED STATES

Nos. 72–394 AND 72–414

Casper W. Weinberger, Secretary of Health, Education, and Welfare, et al., Petitioners, 72–394 *v.* Hynson, Westcott and Dunning, Incorporated.	On Writs of Certiorari to the United States Court of Appeals for the Fourth Circuit.
Hynson, Westcott and Dunning, Incorporated, Petitioner, 72–414 *v.* Casper W. Weinberger, Secretary of Health, Education, and Welfare, et al.	

[June 18, 1973]

MR. JUSTICE DOUGLAS delivered the opinion of the Court.

These cases, together with *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, *post*, at —, *CIBA Corp.* v. *Weinberger*, *post*, at —, and *USV Pharmaceutical Corp.* v. *Weinberger*, *post*, at —, all here on certiorari, raise a series of questions under the 1962 amendments[1] to the Federal Food, Drug, and Cosmetic Act of 1938. 52 Stat. 1040. The 1938 Act, which established a system of premarketing clearance for drugs, prohibited the introduction into commerce of any "new drug" unless a new drug application (NDA) filed with the Food and Drug Administration

[1] Drug Amendments of 1962 (Harris-Kefauver Act), 76 Stat. 780, amending 21 U. S. C. § 301 *et seq.*

(FDA) [2] was effective with respect to that drug. § 505 (a). 52 Stat. 1052. Under the 1938 Act a "new drug" was one not generally recognized by qualified experts as safe for its intended use. § 201 (p)(1). The Government could sue to enjoin violations, prosecute criminally, and seize and condemn the articles. §§ 301 (d), 302 (a), 303, 304. The Act established procedures for filing new drug applications, § 505 (b), and provided standards under which, after notice and hearing, FDA could refuse to allow an NDA to become effective, §§ 505 (c) and (d), or could suspend an NDA in effect on the basis of new evidence that the drug was unsafe. § 505 (e). Orders denying or suspending an NDA could be reviewed in a district court on the administrative record. § 505 (h).

The 1962 Act amended § 201 (p)(1) of the 1938 Act to define a "new drug" as a drug not generally recognized among experts as *effective* as well as safe for its intended uses. 21 U. S. C. § 321 (p)(1). A new drug, as now defined, still may not be marketed unless an NDA is in effect. FDA is now directed to refuse approval of an NDA and to withdraw any prior approval if "substantial evidence" [3] that the drug is effective for its intended use is

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[2] The Act originally provided for filing applications with the Secretary of Agriculture, but his functions were assigned to the FDA. The FDA is now part of the Department of Health, Education, and Welfare (HEW), and the Secretary of HEW has delegated his responsibilities under the Federal Food, Drug, and Cosmetic Act to the Commissioner of Food and Drugs. 21 CFR § 2.120.

[3] "Substantial evidence" was defined to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have . . . ." 21 U. S. C. § 355 (d).

lacking. 21 U. S. C. §§ 355 (d) and (e). Thus, the basic clearance system, requiring FDA approval of an NDA before a "new drug" may be lawfully marketed, was continued, except that FDA now either must approve or disapprove an application within 180 days. 21 U. S. C. § 355 (c). (Under the 1938 Act an application automatically became effective if it was not disapproved.) Judicial review was transferred to the courts of appeal. 21 U. S. C. § 355 (h).

Since the Act as amended requires affirmative agency approval, all NDAs "effective" prior to 1962 were deemed "approved" under the new definition, and manufacturers were given two years to develop substantial evidence of effectiveness during which previously approved NDAs could not be withdrawn by FDA for a drug's lack of effectiveness.[4] The 1962 amendments also contain a "grandfather" clause exempting from the effectiveness requirements any drug which on the day preceding enactment (1) was commercially used or sold in the United States, (2) was not a "new drug" as defined in the 1938 Act (it being generally recognized as safe) and (3) "was not covered by an effective application" for a new drug under the 1938 Act.[5]

Between 1938 and 1962 FDA had permitted 9,457 NDAs to become effective. Of these some 4,000 were still on the market. In addition, there were thousands of drugs which manufacturers had marketed without applying to the FDA for clearance. These drugs, known as "me-toos," are similar to or identical with drugs with effective NDAs and are marketed in reliance on the "pioneer" drug application approved by the FDA. In some cases, a manufacturer obtained an advisory opinion

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[4] Drug Amendments of 1962, §§ 107 (c)(2) and (c)(3)(B), 76 Stat. 788–789, note following 21 U. S. C. § 321 (1970 ed.).

[5] *Id.*, § 107 (c)(4).

letter from the FDA that its product was generally recognized among experts as safe.

To aid in its task of fulfilling the statutory mandate to review all marketed drugs for their threapeutic efficacy, whether or not previously approved, the FDA retained the National Academy of Sciences-National Research Council (NAS–NRC) to create expert panels to review by class the efficacy of each approved drug. Holders of NDAs were invited to furnish the panels with the best available data to establish the effectiveness of their drugs.[6] The panels reported to FDA; and on January 23, 1968, the FDA announced its policy of applying the NAS–NRC efficacy findings to all drugs, including the related "me-too" drugs.[7]

I

Respondent in No. 394, Hynson, Wescott and Dunning, Inc., had filed an application under the 1938 Act for a drug called Lutrexin, recommended by Hynson for use in the treatment of premature labor, threatened and habitual abortion, and dysmenorrhea. FDA informed Hynson that Hynson's studies submitted with the application were not sufficiently well controlled to justify the claims of effectiveness and urged Hynson not to represent the drug as useful for threatened and habitual abortion. But the FDA allowed the application to become effective, since the 1938 Act permitted evaluation of a new drug solely on the grounds of its *safety*. Before the 1962 amendments

[6] 31 Fed. Reg. 9426.

[7] The FDA has recently adopted a regulation declaring the manner in which Drug Efficacy Study Implementation (DESI) Notices and Notices of Opportunity for Hearing apply to identical, related, and similar drugs. Any person with an interest in such drugs are provided an opportunity for hearing on any proposed withdrawal of NDA approval for the basic or pioneer drug. 37 Fed. Reg. 23185, adding § 130.40 to 21 CFR.

Hynson filed an application for a related drug which the FDA, again on the basis of the test of *safety*, allowed to become effective. When the 1962 amendments became effective and NAS–NRC undertook to appraise the efficacy of drugs theretofore approved as safe, Hynson submitted a list of literature references, a copy of an unpublished study, and a representative sample testimonial letter on behalf of Lutrexin. The panel of NAS–NRC working in the relevant field reported to FDA that Hynson's claims for effectiveness of the drug were either inappropriate or unwarranted in the absence of submission of further appropriate documentation. At the invitation of the Commissioner on Food and Drugs, Hynson submitted additional data. But the Commissioner concluded that this additional information was inadequate and published notice of his intention to withdraw approval of the NDAs covering the drug, offering Hynson the opportunity for a prewithdrawal hearing. Before the hearing could take place, Hynson brought suit in the District Court for a declaratory judgment that the drugs in question were exempt from the *efficacy* review provisions of the 1962 amendments or, alternatively, that there was no lack of substantial evidence of the drug's *efficacy*. The Government's motion to dismiss was granted, the District Court ruling that FDA had primary jurisdiction and that Hynson had failed to exhaust its administrative remedies.

While the District Court litigation was pending, FDA promulgated new regulations establishing minimal standards for "adequate and well-controlled investigations" and limiting the right to a hearing to those applicants who could proffer at least some evidence meeting those standards.[8] Although Hynson maintained that it was not subject to the new regulations because its initial request for a hearing predated their issuance, it renewed

[8] 35 Fed. Reg. 7251, amending 21 CFR §§ 130.12 (a) (5) and 130.14.

its request and submitted the material which it claimed constituted "substantial evidence" of Lutrexin's effectiveness. The Commissioner denied the request for a hearing and withdrew the NDA for Lutrexin. He ruled that Lutrexin is not exempt from the 1962 amendments and that Hynson had not submitted adequate evidence that Lutrexin is not a new drug or is effective. The Court of Appeals reversed, 461 F. 2d 215, holding that while the drugs in question were not exempt, Hynson was entitled to a hearing on the substantial evidence question.

Section 505 (e) [9] directs the FDA to withdraw approval of an NDA if the manufacturer fails to carry the burden of showing there is "substantial evidence" [10] respecting the *efficacy* of the drug. As the Court of Appeals says, "substantial evidence" was substituted for "preponderance" of the evidence. 461 F. 2d, at 220. The Act and the Regulations, in their reduction of that standard to detailed guidelines,[11] make the FDA's so-called administrative summary judgment procedure appropriate.

The general contours of "substantial evidence" are defined by § 505 (d) of the Act to include "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by

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[9] Section 505 (e) as amended, 21 U. S. C. § 355 (e), provides in relevant part:

"The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any new drug under this section if the Secretary finds . . . (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; . . ."

[10] See n. 2, *supra*.

[11] 21 CFR § 130.12 (a)(5) as amended, 35 F. R. 7251, is set forth in relevant part in an Appendix to this opinion.

scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." 21 U. S. C. § 355 (d). Acting pursuant to his "authority to promulgate regulations for the efficient enforcement" of the Act, § 701 (a), 21 U. S. C. § 371 (a), the Commissioner has detailed the "principles . . . recognized by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is 'substantial evidence' to support the claims of effectiveness for 'new drugs' . . . ." 21 CFR § 130.12 (a)(5)(ii). They include a "plan or protocol" setting forth the objective of the study and an adequate method for selecting appropriate subjects,[12] explaining the methods of observation and steps taken to minimize bias, providing a comparison by one of four "recognized" methods of the results of treatment or diagnosis with a control, and summarizing the methods of analysis, including any appropriate statistical methods. *Id.*, § 130.12 (a)(5)(ii)(*a*). No investigation will be considered "adequate for approval of a new drug" unless the test drug is "standardized as to identity, strength, quality, and dosage form to give significance to the results of the investigation." *Id.*, § 130.12 (a)(5)(ii)(*b*). Finally, the regulation provides that "[u]ncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims

[12] Subjects must be chosen so that they are "suitable for the purposes of the study," assigned to test groups in such a way as to minimize bias, and comparable in terms of "pertinent variables, such as age, sex, severity, or duration of disease, and use of drugs other than the test drug." 21 CFR § 130.12 (a)(5)(ii)(*a*)(2).

of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support. . . . Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered." *Id.*, § 130.12 (a)(5)(ii)(c).

Lower courts have upheld the validity of these regulations,[13] and it is not disputed here that they express well-established principles of scientific investigation. Moreover, their strict and demanding standards, barring anecdotal evidence indicating that doctors "believe" in the efficacy of a drug, is amply justified by the legislative history. The hearings underlying the 1962 Act show a marked concern that impressions or beliefs of physicians, no matter how fervently believed, are treacherous.[14] Congress wrote in § 505 (d) in its definition of "substantial evidence" the requirement of "evidence consisting of adequate and well-controlled investigations." The Senate Report makes clear that an abrupt departure was being taken from old norms for marketing goods. There had been mounting concern over *efficacy* of drugs as well as their *safety*.[15] The Report stated: [16]

". . . a claim could be rejected if it were found,

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[13] *Upjohn Co.* v. *Finch*, 422 F. 2d 944 (CA6); *Pharmaceutical Manufacturers Assn.* v. *Richardson*, 318 F. Supp. 301 (Del.). The FDA was enjoined from enforcing the regulations as originally issued on September 19, 1969, 34 Fed. Reg. 14596, on the grounds that the FDA had not complied with the notice requirements of the Administrative Procedure Act. *Pharmaceutical Manufacturers Assn.* v. *Finch*, 307 F. Supp. 858 (Del.). The regulations were reissued in their current form on May 8, 1970. 35 Fed. Reg. 7251.

[14] See Hearings on S. 1552 before the Subcomm. on Antitrust and Monopoly of the Senate Comm. on the Judiciary, 87th Cong., 1st Sess., pt. 1, at 195, 282, 411–412. Much of this aspect of the legislative background of the 1962 Act is reviewed in enlightening detail by Judge Latchum in *Pharmaceutical Manufacturers Assn.* v. *Richardson*, *supra*, at 306 *et seq.*

[15] S. Rep. No. 1744, 87th Cong., 2d Sess., pt. 2, at 1.

[16] *Id.*, at 6.

> (a) that the investigations were not 'adequate'; (b) that they were not 'well controlled'; (c) that they had been conducted by experts not qualified to evaluate the effectiveness of the drug for which the application is made; or (d) that the conclusion drawn by such experts could not fairly and responsibly be derived from their investigations."

To be sure, the Act requires the FDA to give "due notice and opportunity for hearing to the applicant" before it can withdraw its approval of an NDA. § 505 (e), 21 U. S. C. § 355 (e). The FDA, however, by regulation, requires any applicant who desires a hearing to submit reasons "why the application . . . should not be withdrawn, together with a well-organized and full-factual analysis of the clinical and other investigational data he is prepared to prove in support of his opposition to the notice of opportunity for a hearing. . . . When it clearly appears from the data in the application and from the reasons and factual analysis in the request for the hearing that there is no genuine and substantial issue of fact . . . , *e. g.*, no adequate and well-controlled clinical investigations to support the claims of effectiveness," the Commissioner may deny a hearing and enter an order withdrawing the application based solely on this data. 21 CFR § 130.14 (b). What the agency has said, then, is that it will not provide a formal hearing where it is apparent at the threshold that the applicant has not tendered *any* evidence which *on its face* meets the statutory standards as particularized by the regulations.

The propriety of such a procedure was decided in *United States* v. *Storer Broadcasting Co.*, 351 U. S. 192, 205, and *Federal Power Commission* v. *Texaco*, 377 U. S. 33, 39. We said in *Texaco:*

> "[T]he statutory requirement for a hearing under § 7 [of the Natural Gas Act] does not preclude the

> Commission from particularizing statutory standards through the rulemaking process and barring at the threshold those who neither measure up to them nor show reasons why in the public interest the rule should be waived." *Ibid.*

There can be no question that to prevail at a hearing an applicant must furnish evidence stemming from "adequate and well-controlled investigations." We cannot impute to Congress the design of requiring, nor does due process demand, a hearing when it appears conclusively from the applicant's "pleadings" that it cannot succeed.[17]

The NAS–NRS panels evaluated approximately 16,500 claims made on behalf of the 4,000 drugs marketed pursuant to effective NDAs in 1962. Seventy percent of these claims were found not to be supported by substantial evidence of effectiveness, and only 434 drugs were found effective for all their claimed uses. If the FDA were required automatically to hold a hearing for each product whose efficacy was questioned by the NAS–NRC

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[17] This applies, of course, only to those regulations that are precise. For example, the plan or protocol for a study must include "a summary of the methods of analysis, and an evaluation of data derived from the study, including any appropriate statistical methods." 21 CFR § 130.12(a)(5)(ii)(*a*)(5). A mere reading of the study submitted will indicate whether the study is totally deficient in this regard. Some of the regulations, however, are not precise, as they call for the exercise of discretion or subjective judgment in determining whether a study is adequate and well-controlled. For example, § 130.12 (a)(5)(ii)(*a*)(2)(i) requires that the plan or protocol for the study include a method of selection of the subjects that "provide *adequate* assurance that they are suitable for the purposes of the study." (Emphasis added.) The qualitative standards "adequate" and "suitable" do not lend themselves to clear-cut definition, and it may not be possible to tell from the face of a study whether the standards have been met. Thus, it might not be proper to deny a hearing of the grounds that the study did not comply with this regulation.

study, even though many hearings would be an exercise in futility, we have no doubt that it could not fulfill its statutory mandate to remove from the market all those drugs which do not meet the effectiveness requirements of the Act.

If this were a case involving trial by jury as provided in the Seventh Amendment, there would be sharper limitations on the use of summary judgment,[18] as our decisions reveal. See, *e. g.*, *Adickes* v. *Kress & Co.*, 398 U. S. 144, 153–161; *White Motor Co.* v. *United States*, 372 U. S. 253. But Congress surely has great leeway in setting standards for releasing on the public, drugs which may well be miracles or, on the other hand, merely easy money-making schemes through use of fraudulent articles labelled in mysterious scientific dress. The standard of "well-controlled investigations" particularized by the Regulations is a protective measure designed to ferret out those drugs for which there is no affirmative, reliable evidence of effectiveness. The drug manufacturers have full and precise notice of the evidence they must present to sustain their NDAs, and under these circumstances we find the FDA hearing regulations unexceptionable on any statutory or constitutional ground.

Our conclusion that the summary judgment procedure of the FDA is valid does not end the matter, for Hynson argues that its submission to the FDA satisfied its threshold burden. In reviewing an order of the Commissioner denying a hearing, a court of appeals must determine whether the Commissioner's findings accurately reflect the study in question and if they do, whether the deficiencies he finds conclusively render the study inadequate

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[18] Under the Rules of Civil Procedure the party moving for summary judgment has the burden of showing the absence of a genuine issue as to any material fact. *Adickes* v. *Kress & Co.*, 398 U. S. 144, 157.

or uncontrolled in light of the pertinent regulations.[19] There is a contrariety of opinion within the Court concerning the adequacy of Hynson's submission. Since a majority are of the view that the submission was sufficient to warrant a hearing, we affirm the Court of Appeals on that phase of the case.

II

No. 414 is a cross-petition by Hynson from the judgment of the Court of Appeals. This cross-petition raises questions concerning the "new drug" provisions of the 1962 amendments. The Court of Appeals suggested that only a district court has authority to determine whether Lutrexin is a "new drug." The Government contends that the Commissioner has authority to determine new drug status in proceedings to withdraw approval of the product's new drug application (NDA) under § 505 (e). Although Hynson agrees, some of the manufacturers, parties to other suits in this group of cases, advance the contrary view.

Prior to 1938 there was no machinery for the premarketing approval of drugs sold in commerce. Under the 1906 Act, 34 Stat. 758, adulterated and misbranded drugs were narrowly defined, and the Act provided only criminal sanctions and seizure by libel for condemnation. As previously noted, the 1938 Act provided for regulatory clearance of drugs prior to marketing and for administrative suspension of any clearance if required in interests

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[19] Under the Administrative Procedure Act, a court reviews agency findings to determine whether they are supported by substantial evidence only in a case subject to the hearing provisions of 5 U. S. C. §§ 556 and 557 or "otherwise reviewed on the record of an agency hearing provided by statute . . . ." This is not such a case. The question with which we are concerned involves the initial agency determination whether a hearing is required by statute. See *Pfizer, Inc.* v. *Richardson*, 434 F. 2d 536, 546–547 (CA2).

of public safety. To introduce a new drug an application had to be effective with respect to that drug. The application was to become effective within a fixed period unless the agency after notice and opportunity for hearing refused to permit it to become effective, finding that it could not determine from existing evidence or had not been shown that it was safe. 52 Stat. 1041–1042, 1052. Any NDA could be suspended if clinical experience or new testing showed that the drug was not safe. *Id.*, 1053. Orders denying or suspending an NDA were reviewable on the administrative record in a district court. *Ibid.* Marketing a new drug without an effective NDA could be enjoined or made the basis of a criminal prosecution, or the drug could be seized in libel and condemnation proceedings.

There was a steady stream of NDAs under that Act supported by voluminous data.[20] Many new drugs claiming "me-too" status were marketed illegally or were launched with an advisory opinion of FDA that they were recognized as safe. It is estimated that by 1969 there were five identical or similar drugs for every drug with an effective NDA. Enormous administrative problems were created. Each NDA contained about 30 volumes, a stack 10 to 12 feet high; and some contained as many as 400 volumes of data.

It is clear to us that the FDA has power to determine whether particular drugs require an approved NDA in order to be sold to the public. The FDA is indeed the administrative agency selected by Congress to administer the Act, and it cannot administer the Act intelligently and rationally unless it has authority to determine what drugs are "new drugs" under § 201 (p) and whether they

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[20] 1939 Annual Report, FDA; 1941 Annual Report FDA; Annual Reports, Federal Security Agency (1938–1952); Annual Reports HEW (1953–1962).

are exempt from the efficacy requirements of the 1962 amendments by the grandfather clause of § 107 (c)(4).

Regulatory agencies have by the requirements of particular statutes usually proceeded on a case-by-case basis, giving each person subject to regulation separate hearings. But there is not always a constitutional reason why that must be done. *United States* v. *Storer Broadcasting Co.*, 351 U. S. 192, is one example. We there upheld rules of the Federal Communications Commission limiting the number of broadcasting stations a single individual might own, saying that that was a proper exercise of the agency's "rule-making authority necessary for the orderly conduct of its business." *Id.*, at 202. The comprehensive rather than the individual treatment may indeed be necessary for quick effective relief. See *Permian Basin Area Rate Cases*, 390 U. S. 747. A generic drug—which is found to be unsafe and/or lacking in efficacy—may be manufactured by several persons or manufacturers. To require separate judicial proceedings to be brought against each, as if each were the owner of a Black Acre being condemned, would be to create delay where in the interests of public health there should be prompt action. A single administrative proceeding in which each manufacturer may be heard is constitutionally permissible measured by the requirements of procedural due process.

FDA maintains that a withdrawal of any NDA approval covers all "me-too" drugs. For the reasons stated that procedure is a permissible one where every manufacturer of a challenged drug has an opportunity to be heard. FDA under § 5 (e) of the Administrative Procedure Act, 5 U. S. C. § 544 (e), may issue a declaratory order governing all drugs covered by a particular NDA. That section prescribes the procedures an agency must follow "in every case of adjudication required by statutes

to be determined on the record after opportunity for an agency hearing." The industry maintains that § 5 (e) is of no avail to FDA because in a withdrawal proceeding a common issue is whether a drug is a "new drug." That issue, it is argued, can be resolved only in a court proceeding where there is an adjudication "on the record of a hearing." But that assumes an individualized hearing and adjudication as is common in regulatory proceedings. Section 5 (e), however, does not place administrative proceedings in that straitjacket. It provides that an agency "in its sound discretion, may issue a declaratory order to terminate a controversy or remove uncertainty." The termination of a controversy over a "new drug" may often be of prime importance. This is an age of ever-expanding dockets at the administrative as well as at the judicial level. If the administrative controls over drugs are to be efficient, they must be exercised with dispatch. Only paralysis would result if case-by-case battles in the courts were the only way to protect the public against unsafe or ineffective drugs. Moreover, if every "me-too" drug in a particular generic category had to be put to the test in court actions, great inequities might well result. It might take months to eliminate one "me-too" drug manufactured by one company from the market. Meanwhile, competitors selling drugs in the same category would go scot-free until the tedious and laborious procedures of litigation reached them. We cannot believe that Congress engaged in such an exercise in futility when it enacted the 1962 amendments. That would in effect restore the enforcement provisions to the status they enjoyed under the rather primitive 1906 Act. We hold that FDA by reasons of § 5 (e) of the Administrative Procedure Act may issue a declaratory order to terminate a controversy over a "new drug" or to remove any uncertainty whether a par-

ticular drug is a "new drug" within the meaning of § 201 (p)(1) of the Act. See *Abbott Laboratories* v. *Gardner*, 387 U. S. 136.

It is argued, however, that the only lawful purpose of an FDA hearing is to allow it a method for determining which lawsuits it will file in the future. Yet that is only another version of the tactics of delay and procrastination which the industry offers as the way best to serve industry's needs. The public needs are, however, opposed and paramount. We do not accept the invitation to hold that FDA has no jurisdiction to determine whether a particular drug is a "new drug" and to decide whether an NDA should be withdrawn.

Its determination that a product is a "new drug" or a "me-too" drug is, of course, reviewable. But its jurisdiction to determine whether it has jurisdiction is as essential to its effective operation as is a court's like power. Cf. *United States* v. *Shipp*, 203 U. S. 563, 573. The heart of the new procedures designed by Congress is the grant of primary jurisdiction to FDA, the expert agency it created. FDA does not have the final say, for review may be had not in a district court (except in a limited group of cases we will discuss), but in a court of appeals. FDA does not have unbridled discretion to do what it pleases. It procedures must satisfy the rudiments of fair play. Judicial relief is available only after administrative remedies have been exhausted.

It is argued that though FDA is empowered to decide the threshold question whether the drug is a "new drug," that power is only an incident to its power to approve or withdraw approval of NDAs. Some manufacturers, however, have no NDAs in effect and are not seeking approval of any drugs. Nevertheless, FDA may make a declaratory order that a drug is a "new drug." While that order is not reviewable in the Court of Appeals under § 505 (h), it is reviewable by the District Court

under the Administrative Procedure Act. 5 U. S. C. §§ 701–704; *Citizens to Preserve Overton Park* v. *Volpe*, 401 U. S. 402, 410; *Abbott Laboratories* v. *Gardner*, *supra*, at 139–148. By analogy an agency order declaring a commodity not exempt from regulation is normally a declaratory order that is reviewable, as we held in *Frozen Food Express* v. *United States*, 351 U. S. 40.

The question then presented is whether FDA properly exercised its jurisdiction in this case. As indicated above, Hynson in requesting an administrative hearing also asked FDA to decide that Lutrexin is not a "new drug" within the meaning of § 201 (p) as amended, 21 U. S. C. § 321 (p).[21] In addition, it asked that Lutrexin be "grandfathered" under § 107 (c)(4) of the 1962 amendments.[22] The Commissioner rejected both claims.

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[21] That section provides:

"The term 'new drug' means—

"(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a 'new drug' if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

"(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."

[22] That section provides:

"In the case of any drug which, on the first day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section

Finding that Hynson had failed to present any evidence of adequate and well-controlled investigations in support of Lutrexin's effectiveness, he concluded that "there is no data base upon which experts can fairly and responsibly conclude that the safety and effectiveness of the drugs has been proven and is so well established that the drugs can be generally recognized among such experts as safe and effective for their intended uses." The Commissioner also held that Lutrexin is not exempt under § 107 (c)(4) because its NDA, which had become effective in 1953, had not been withdrawn prior to the enactment of the 1962 amendments and thus was "covered by an effective application" within the meaning of § 107 (c)(4)(C). The Court of Appeals affirmed the Commissioner's ruling that Lutrexin is not exempt under § 107 (c)(4). It did not discuss his holding that Lutrexin currently is a "new drug." Although we agree that the Commissioner properly ruled that Lutrexin does not come within § 107 (c)(4), we conclude that the Commissioner's order with respect to Lutrexin's "new drug" status must be vacated.

The thrust of § 201 (p) is both qualitative and quantitative. The Act, however, nowhere defines what constitutes "general recognition" among experts. Hynson contends that the "lack of substantial evidence" is applicable only to proof of the *actual* effectiveness of drugs that fall within the definition of a new drug and not to the initial determination under § 201 (p) whether a drug is "generally recognized" as effective. It would rely solely on the testimony of physicians and the extant

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201 (p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201 (p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day."

literature, evidence that has been characterized as "anecdotal." We agree with FDA, however, that the statutory scheme and overriding purpose of the 1962 amendments compel the conclusion that the hurdle of "general recognition" of effectiveness requires at least "substantial evidence" of effectiveness for approval of an NDA. In the absence of any evidence of adequate and well-controlled investigation supporting the efficacy of Lutrexin, *a fortiori* Lutrexin would be a "new drug" subject to the provisions of the Act.[23]

As noted, the 1962 amendments for the first time gave FDA power to scrutinize and evaluate drugs for effectiveness as well as safety. The Act requires FDA to disapprove any application when there is a lack of "substantial evidence" that the applicant's drug is effective. § 505 (d), 21 U. S. C. § 355 (d). Similarly, he may withdraw approval for any drug if he subsequently determines that there is a lack of such evidence. § 505 (e), 21 U. S. C. § 355 (e). Evidence may be accepted only if it consists of "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved . . . . § 505 (d), 21 U. S. C. § 355 (d). The legislative history of the Act indicates that the test was to be a rigorous one. The "substantial evidence" requirement reflects the conclusion of Congress, based upon hearings,[24] that clinical impressions of practicing physicians and poorly controlled experiments do not constitute an adequate basis for establishing efficacy. This policy underlies the regulations defining the contours of "substantial evidence": "Uncontrolled studies

[23] It also follows that if Hynson were not entitled to a hearing under § 505 (e), it would not be entitled to a hearing on its claim that Lutrexin is not a "new drug."

[24] See Hearings, *supra*, n. 14.

or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support of well-controlled studies . . . . Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered." 21 CFR § 130.12 (a)(5)(ii)(*c*).

These efficacy requirements were not designed to be prospective only. Clearly, after the initial two-year moratorium on existing drugs, FDA has the power to withdraw an application which became effective prior to the adoption of the 1962 amendments, if the applicant has not provided "substantial evidence" of the drug's efficacy. The Act plainly contemplates that such drugs will be evaluated on the basis of adequate and well-controlled investigations. Hynson would have us hold that withdrawal proceedings can be thwarted by a showing of general recognition of effectiveness based merely on expert testimony and reports with respect to investigations and clinical observation regardless of the controls used. But, we cannot construe § 201 (p) to deprive FDA of jurisdiction over a drug which, if subject to FDA regulation, could not be marketed because it had not passed the "substantial evidence" test. To do so "would be to impute to Congress a purpose to paralyze with one hand what it sought to promote with the other." *Clark* v. *Uebersee Finanz-Korp.*, 332 U. S. 480, 489.

Moreover, the interpretation of § 201 (p) urged by Hynson is not consistent with the statutory scheme as it operates on a purely prospective basis. Under subsection (2), a drug cannot transcend "new drug" status until it has been used "to a material extent or for a material time." Yet, a drug cannot be marketed lawfully before an NDA has been approved by the Commissioner on the

basis of "substantial evidence." As the Solicitor General argues, "the Act is designed so that drugs on the market, unless exempt, will have mustered the requisite scientifically reliable evidence of effectivness long before they are in a position to drop out of active regulation by ceasing to be a 'new drug.'"

It is well established that our task in interpreting separate provisions of a single Act is to give the Act "the most harmonious, comprehensive meaning possible" in light of the legislative policy and purpose. *Id.*, at 488; see *United States* v. *An Article of Drug . . . Bacto-Unidisk*, 394 U. S. 784, 798. We accordingly have concluded that a drug can be "generally recognized" by experts as effective for intended use within the meaning of the Act only when that expert consensus is founded upon "substantial evidence" as defined in § 505 (d). We have held in No. 394, however, that the Commissioner was not justified in withdrawing Hynson's NDA without a prior hearing on whether Hynson had submitted "substantial evidence" of Lutrexin's effectiveness. Consequently, any ruling as to Lutrexin's "new drug" status is premature and must await the outcome of this hearing.

Finally, we cannot agree with Hynson that Lutrexin is exempt from the provisions of the Act by virtue of § 107 (c)(4) of the 1962 amendments. That section provides that no drug will be treated as a "new drug" if, on the day preceding the adoption of the amendments, the drug "(A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201 (p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act . . . ." The applicability of this section turns solely on whether Lutrexin was "covered" by an effective NDA immediately prior to the adoption of the 1962 amendments. Hynson argues that when Lutrexin became gen-

erally recognized as safe and was no longer a "new drug," its NDA ceased to be effective.[25]

That argument draws no statutory support. The 1938 Act did not provide any mechanism, other than the Commissioner's suspension authority under § 505 (e), whereby an NDA once effective could cease to be effective. Indeed, § 505 (e) leads to the conclusion that an NDA remains effective unless it is suspended. That section empowers FDA to withdraw approval of an NDA whenever new evidence comes to light suggesting that the drug has become unsafe, whether or not the drug was generally recognized as safe in the interim.

Moreover, Hynson's argument, as the Court of Ap-

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[25] Hynson also argues that Lutrexin is exempt by operation of § 107 (c)(2), which provides:

"An application filed pursuant to section 505 (b) of the basic Act which was 'effective' within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application 'approved' by the Secretary within the meaning of the basic Act as amended by this Act."

Hynson contends that Lutrexin, generally recognized as safe prior to 1962, was not a "new drug" under applicable standards before the 1962 amendments. Thus, the argument goes, its NDA had ceased to be effective and could not be deemed "approved" under § 107 (c)(2). Consequently, there was no approval that could be withdrawn in administrative proceedings pursuant to § 505 (e).

This argument shares a common thread with the argument under § 107 (c)(4)—that the NDA for Lutrexin had ceased to be effective. The argument is no more persuasive under § 107 (c)(2) than § 107 (c)(4). In addition, the construction offered by Hynson would upset the carefully drawn transitionary provisions of §§ 107 (c)(2) and (c)(3). Since the Commissioner now must affirmatively approve or disapprove all NDAs, § 107 (c)(2) was enacted to remove the administrative burden of approving each and every NDA then effective. It also protected the market authority of all manufacturers that had effective NDAs. Without this provision, no manufacturer whose drug had become generally recognized as safe could have continued to market the drug if it was not also generally recognized as effective.

peals recognized, would render clause (C) superfluous. Under Hynson's reasoning, any drug that could satisfy clause (B)—*i. e.*, any drug that had become generally recognized as safe—automatically would satisfy clause (C). This construction, therefore, offends the well-settled rule of statutory construction that all parts of a statute, if at all possible, are to be given effect. See, *e. g.*, *Jarecki* v. *G. D. Searle & Co.*, 367 U. S. 303, 307; *Ginsberg & Sons* v. *Popkin*, 285 U. S. 204, 208. The interpretation accorded by the Commissioner and the Court of Appeals, on the other hand, does give clause (C) operative effect. It would limit the exemption to drugs, generally recognized as safe, which had not come under the blanket of an effective NDA. This interpretation accords with the legislative history which suggests that the exemption is afforded only for drugs that never had been subject to new drug regulation.[26]

Except with the modification with respect to Lutrexin's "new drug" status, the judgment of the Court of Appeals is

Affirmed.

MR. JUSTICE BRENNAN took no part in the consideration or decision of these cases. MR. JUSTICE STEWART took no part in the decision of these cases.

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[26] See S. Rep. No. 1744, 87th Cong., 2d Sess., pt. 2, at 8; H. R. Rep. No. 2464, 87th Cong., 2d Sess., 12; H. R. Rep. No. 2526, 87th Cong., 2d Sess., 22–23. Hynson contends that the construction afforded by FDA renders the exemption nugatory and defeats the legislative purpose. The provision, however, does exempt drugs that, as a generic class, were never subject to new drug regulation. These consist primarily of over-the-counter drugs which, although they were not "grandfathered" under the 1938 Act, were not subject to new drug regulation because of universal recognition of the safety of their old, established ingredients at the time they came on the market.

21 CFR § 130.12 (a)(5)(ii) provides:

(ii) The following principles have been developed over a period of years and are recognised by the scientific community as the essentials of adequate and well-controlled clinical investigations. They provide the basis for the determination whether there is "substantial evidence" to support the claims of effectiveness for "new drugs" and antibiotic drugs.

(a) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:

(1) A clear statement of the objectives of the study.

(2) A method of selection of the subjects that—

(i) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired.

(ii) Assigns the subjects to test groups in such a way as to minimize bias.

(iii) Assures comparability in test and control groups of pertinent variables, such as age, sex, severity, or duration of disease, and use of drugs other than the test drug.

(3) Explains the methods of observation and recording of results, including the variables measured, quantitation, assessment of any subjective response, and steps taken to minimize bias on the part of the subject and observer.

(4) Provides a comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. Level and methods of "blinding," if used, are to be documented. Generally, four types of comparison are recognized:

(*i*) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated patients.

(*ii*) Placebo control: Comparison of the results of use of the new drug entity with an inactive preparation designed to resemble the test drug as far as possible.

(*iii*) Active treatment control: An effective regimen of therapy may be used for comparison, e. g., where the condition treated is such that no treatment or administration of a placebo would be contrary to the interest of the patient.

(*iv*) Historical control: In certain circumstances, such as those involving diseases with high and predictable mortality (acute leukemia of childhood), with signs and symptoms of predictable duration or severity (fever in certain infections), or, in case of prophylaxis, where morbidity is predictable, the results of use of a new drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable patients or populations with no treatment or with a regimen (therapeutic, diagnostic, prophylactic) the effectiveness of which is established.

(5) A summary of the methods of analysis, and an evaluation of data derived from the study, including any appropriate statistical methods.

Provided, however, That any of the above criteria may be waived in whole or in part, either prior to the investigation or in the evaluation of a completed study, by the Director of the Bureau of Drugs with respect to a specific clinical investigation; a petition for such a waiver may be filed by any person who would be adversely affected by the application of the criteria to a particular clinical investigation; the petition should show that some or all of the criteria are not reasonably applicable to the investigation and that alternative procedures can be, or have been, followed, the results of which will or have yielded data that can and should be accepted as substantial evidence of the drug's effectiveness. A petition for a waiver shall set forth clearly and concisely the specific provision or provisions in the criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been, employed, what results have been obtained, and the basis on which it can be, or has been, concluded that the clinical investigation will or has yielded substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(*b*) For such an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(*c*) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide

corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

SUPREME COURT OF THE UNITED STATES

Nos. 72–394 AND 72–414

Casper W. Weinberger, Secretary of Health, Education, and Welfare, et al., Petitioners, 72–394 *v.* Hynson, Westcott and Dunning, Incorporated.	On Writs of Certiorari to the United States Court of Appeals for the Fourth Circuit.
Hynson, Westcott and Dunning, Incorporated, Petitioner, 72–414 *v.* Casper W. Weinberger, Secretary of Health, Education, and Welfare, et al.	

[June 18, 1973]

MR. JUSTICE POWELL, concurring in part, and concurring in the result in part.

I concur in Part II of the Court's opinion, which disposes of the issues raised by Hynson, Westcott and Dunning, Incorporated, in its cross-petition (No. 72–414). As to Part I, which addresses issues raised in the petition filed by the Commissioner of FDA (No. 72–394), I concur only in the result and state briefly the limited sense in which I accept the Court's conclusion.

Insofar as the Court today sustains the holding below that Hynson's submission to FDA raised "a genuine and substantial issue of fact" requiring a hearing on the ultimate issue of efficacy, 21 CFR § 130.14 (b) (1970), I am in accord. Hynson's presentation in support of the efficacy of Lutrexin clearly justified a hearing as to whether the drug was supported by "adequate and well

controlled investigations," 21 U. S. C. § 355 (d), even as that term is defined in the Commission's regulations. 21 CFR § 130.12 (a)(5) (1970). For this reason I concur in the result reached in this case. I cannot agree on this record, however, with any implications or conclusions in the Court's opinion to the effect that the regulations—as construed and applied by the Commissioner in this case—are either compatible with the statutory scheme or constitutional under the Due Process Clause.[1] Such questions have not been squarely presented in this case and, in light of the Court's conclusion that Hynson has complied with the regulations, their resolution is unnecessary to the Court's decision.

Were we required to reach these issues, there may well be serious doubt whether the Commissioner's rigorous threshold specifications as to proof of "adequate and well controlled investigations," coupled with his restrictive summary judgment regulation, go beyond the statutory requirements and in effect frustrate the congressional mandate for a prewithdrawal "opportunity for hearing." 21 U. S. C. § 355 (e). There is also a genuine issue of procedural due process where, as in this case, the Commissioner construes his regulations to deny a hearing as to the efficacy of a drug established and used by the medical profession for two decades, and where its effectiveness is supported by a significant volume of clinical data and the informed opinions of experts whose qualifications are not questioned.[2]

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[1] Cf. *Fuentes* v. *Shevin*, 407 U. S. 67, 80 (1970), and cases cited therein. I do not question, of course, the authority of the Commissioner to adopt reasonable regulations consistent with the statute and which do not, as applied, deprive persons of their property without the elementary due process of a fair opportunity for a hearing.

[2] There can be no doubt, both from the legislative history and the language of the 1962 amendments to the Act, that Congress intended

These important and complex questions should await decision in future cases in which the issues are briefed fully and are necessary to the Court's decision.

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to impose standards that would bar reliance upon anecdotal evidence or mere professions of belief by doctors as determinative of a drug's efficacy. But it is also clear that Congress intended to protect against the arbitrary withdrawal or withholding of approval of a drug where there is "substantial evidence" of its effectiveness. To provide protection against such action, especially when authority is vested in an official who acts in an administrative as well as judicial capacity, the Act specifically provides for a hearing. The public interest is twofold: (i) to remove from the market, in accordance with due process, drugs of no utility or effectiveness; and (ii) to retain on the market those drugs that are efficacious. In an understandable zeal to remove the former, an administrative agency must not overlook both the interest of the public and the right of the proprietor in protecting the drugs that are useful in the prevention, control or treatment of illness.

NOTE: Where it is feasible, a syllabus (headnote) will be released, as is being done in connection with this case, at the time the opinion is issued. The syllabus constitutes no part of the opinion of the Court but has been prepared by the Reporter of Decisions for the convenience of the reader. See *United States* v. *Detroit Lumber Co.*, 200 U.S. 321, 337.

SUPREME COURT OF THE UNITED STATES

Syllabus

CIBA CORP. *v.* WEINBERGER ET AL.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE THIRD CIRCUIT

No. 72-528. Argued April 17, 1973—Decided June 18, 1973

Petitioner manufactures a drug called Ritonic Capsules, for which it filed a new drug application (NDA) that became effective in 1959, on the basis of the drug's safety. After the enactment of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act, the Food and Drug Administration (FDA) withdrew approval of the NDA on the ground that there was no substantial evidence that the drug was *effective* as claimed, under § 505 of the Act. Petitioner sought review of the withdrawal order in the Court of Appeals for the Second Circuit, as provided in § 505 (h), and that court affirmed the order. Prior to the issuance of the withdrawal order petitioner sought declaratory and injunctive relief in the New Jersey District Court, which granted the Government's motion to dismiss the complaint for lack of jurisdiction. The Court of Appeals for the Third Circuit affirmed, holding that the FDA was authorized to decide the jurisdictional question as an incident of its power to approve or withdraw approval for NDA's, that its decision was reviewable on direct appeal by a court of appeals, and since the Court of Appeals for the Second Circuit had ruled against petitioner on that appeal, the jurisdictional issue could not be relitigated in a separate suit for a declaratory judgment. *Held:*

1. The FDA has jurisdiction in an administrative proceeding to determine whether a drug product is a "new drug" within the meaning of § 201 (p) of the Act. *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, *post*, p. —. P. 3.

2. While the Act provides FDA with sanctions, such as civil injunction proceedings, criminal penalties, *in rem* seizure and condemnation, to enforce the prohibition against sale in commerce of any article in violation of § 505, the Act does not create a dual system, one administrative and the other judicial. P. 3.

Syllabus

3. Where petitioner had an opportunity to litigate the "new drug" issue before the FDA and to raise the issue on appeal to a court of appeals, it may not relitigate the issue in another proceeding. P. 4.

463 F. 2d 225, affirmed.

DOUGLAS, J., delivered the opinion of the Court, in which all Members joined, except BRENNAN, J., who took no part in the consideration or decision of the case, and STEWART, J., who took no part in the decision of the case.

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SUPREME COURT OF THE UNITED STATES

No. 72-528

CIBA Corporation, Petitioner,
v.
Caspar W. Weinberger, Secretary of Health, Education, and Welfare, et al.

On Writ of Certiorari to the United States Court of Appeals for the Third Circuit.

[June 18, 1973]

MR. JUSTICE DOUGLAS delivered the opinion of the Court.

Petitioner manufactures a drug called Ritonic Capsules* for which it filed an NDA that became effective in 1959. Under the Act then in force an NDA for a "new drug" required the manufacturer to submit to FDA adequate proof of the drug's safety. This particular NDA became effective on the basis of the drug's safety. As we have noted in the companion cases the 1962 amendments to the Federal Food, Drug and Cosmetic Act of 1938 directed FDA to withdraw approval for NDAs which became effective prior to that time if after notice and opportunity for hearing, it is found that there is a lack of "substantial evidence" that the drug involved is *effective* as claimed in its labeling. And as we have noted, "substantial evidence" as used in the Act, § 505 (d) and § 505 (e)(3), means "adequate and well-controlled in-

*It is a prescription drug recommended "for patients who are losing their drive, alertness, vitality and zest for living because of the natural degenerative changes of advancing years"; and for patients who are "debilitated or depressed by chronic illness, overwork, etc., as well as those recuperating from illness or surgery."

vestigations" from which experts may conclude that the drug will have the claimed effect.

A panel of NAS–NRC reviewed the claims made for ritonic capsules and found it "ineffective" for each of the claims. FDA concluded there was a lack of substantial evidence of their efficacy and gave notice of its intent to withdraw the NDA, offering petitioner an opportunity to submit the required kind of data bearing on the efficacy of the drug and stating that withdrawal of approval of the NDA would cause the ritonic capsules to be a "new drug" for which no NDA was in effect, thereby making future sales unlawful.

Petitioner responded, submitting data on the issue of efficacy and maintained that ritonic capsules was not a "new drug" for purposes of the Act as amended. FDA concluded that petitioner's evidence was insufficient to establish effectiveness and gave notice of a hearing on the withdrawal of the NDA. Petitioner responded, contested FDA's authority to proceed further, and claimed that the product was not a "new drug" under the 1952 Act. It reserved the right to establish its position in the administrative proceedings, in judicial proceedings, or in both. Petitioner filed no more data to support its position; and accordingly FDA withdrew approval of the NDA on the ground that there was no substantial evidence that the drug was effective as claimed. Petitioner sought review of the withdrawal order in the Court of Appeals for the Second Circuit, as provided in § 505 (h). The Court of Appeals affirmed the withdrawal order. *Ciba-Geigy Corp.* v. *Richardson*, 446 F. 2d 466.

Meanwhile, and prior to the issuance of the withdrawal order, petitioner brought suit in the New Jersey District Court seeking declaratory and injunctive relief. After hearing the District Court granted the Govern-

ment's motion to dismiss the complaint for lack of jurisdiction. On appeal the Third Circuit Court of Appeals affirmed, 463 F. 2d 225, holding that FDA was authorized to decide the jurisdictional question as an incident of its power to approve or withdraw approval for NDAs, that its decision on that issue was reviewable on direct appeal by a court of appeals, and since the Second Circuit Court of Appeals had ruled against petitioner on that appeal, the jurisdictional question could not be relitigated in a separate suit for a declaratory judgment. We affirm the Court of Appeals.

We have stated in the *Bentex* case our reasons for concluding that FDA has jurisdiction in an administrative proceeding to determine whether a drug product is a "new drug" within the meaning of § 201 (p) of the Act. A decision that FDA lacks authority to determine in its own proceedings the coverage of the Act it administers, subject of course to judicial review, would seriously impair FDA's ability to discharge the responsibilities placed on it by Congress. As we said in the *Hynson* cases and the *Bentex* case, *ante*, the definition of "new drug" as used in § 3201 (p)(1) involves a determination of technical and scientific questions by experts. The agency is therefore appropriately the arm of Government to make the threshold determination of the issue of coverage. Cf. *Oklahoma Press Publishing Co.* v. *Walling*, 327 U. S. 186, 210–211, n. 47.

It is of course true that the Act gives FDA a second line of defense—civil injunction proceedings, criminal penalties, and *in rem* seizure and condemnation. See §§ 302 (a), 303, 304. Those are sanctions to enforce the prohibition of the Act against the sale in commerce of any article in violation of § 505. But the Act does not create a dual system of control—one administrative, and the other judicial. Cases may arise where there has been no formal administrative determination of the "new

drug" issue, it being first tendered to a district court. Even then, however, the District Court might well stay its hand, awaiting an appropriate administrative determination of the threshold question. See the *Bentex* case, *ante*. Where there is, however, an administrative determination, whether it be explicit or implicit in the withdrawal of an NDA, the tactic of "reserving" the threshold question (the jurisdictional issue) for later judicial determination is not tolerable. There is judicial review of FDA's ruling. But petitioner, having an opportunity to litigate the "new drug" issue before FDA and to raise the issue on appeal to a court of appeals, may not relitigate the issue in another proceeding. *Yakus* v. *United States*, 321 U. S. 414, 444–446.

Affirmed.

MR. JUSTICE BRENNAN took no part in the consideration or decision of this case. MR. JUSTICE STEWART took no part in the decision of this case.

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SUPREME COURT OF THE UNITED STATES

Syllabus

UNITED STATES ET AL. *v.* STUDENTS CHALLENGING REGULATORY AGENCY PROCEDURES (SCRAP) ET AL.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

No. 72–535. Argued February 28, 1973—Decided June 18, 1973*

The Interstate Commerce Act permits railroads to file proposed freight rate increases, with at least 30 days' notice to the Interstate Commerce Commission (ICC) and the public before putting the new rates into effect. The ICC may, pursuant to § 15 (7) of the Act, suspend the operation of the proposed rates for as long as seven months, in order to investigate the lawfulness of the rates. At the end of the seven-month period, the carrier may put the suspended rates into effect unless the ICC has completed its investigation and found the rates unlawful. Proceeding under the statutory scheme, substantially all the Nation's railroads sought a 2.5% surcharge on nearly all freight rates, as an emergency measure to obtain increased revenues pending adoption of selective rate increases on a permanent basis. Shippers, competing carriers, and other interested persons requested the ICC to suspend the tariff for the statutory seven-month period. Various environmental groups, including Students Challenging Regulatory Agency Procedures (SCRAP) and the Environmental Defense Fund (EDF), appellees here, protested that failure to suspend the surcharge would cause their members "economic, recreational and aesthetic harm," and specifically, that the new rate structure would discourage the use of "recyclable" materials and promote the use of raw materials that compete with scrap, thus adversely affecting the environment. On February 1, 1972, the ICC issued an order

*Together with No. 72–562, *Aberdeen & Rockfish Railroad Co. et al.* v. *Students Challenging Regulatory Agency Procedures (SCRAP) et al.*, also on appeal from the same court.

announcing its decision not to suspend the surcharge for the seven-month period, and on April 24, 1972, ordered the proposed selective increases filed by the carriers to be suspended for the full seven-month period ending November 30, 1972, and permitted the collection of the surcharge until that date. SCRAP filed the present suit seeking, *inter alia*, an injunction to restrain enforcement of the February 1 and April 24 orders allowing the carriers to collect the surcharge. SCRAP, an unincorporated association formed by five law students to enhance the quality of the environment, claimed that its members "suffered economic, recreational and aesthetic harm directly as a result of the adverse environmental impact of the railroad freight structure," that each of its members was caused to pay more for finished products, that each of its members uses the forests, rivers, mountains, and other natural resources of the Washington area and at his legal residence for camping, hiking, fishing, and other purposes, and that these uses have been adversely affected by increased freight rates. The main thrust of SCRAP's complaint was that the ICC's orders were unlawful for failure to include a detailed environmental impact statement as required by § 102 (C) of the National Environmental Policy Act of 1969 (NEPA), 42 U. S. C. § 4332(C). The three-judge District Court found that appellees had standing to sue. The court held that its power to grant an injunction was not barred by *Arrow Transportation Co.* v. *Southern R. Co.*, 372 U. S. 658, because NEPA "implicitly confers authority on the federal courts to enjoin *any* federal action taken in violation of NEPA's procedural requirements . . . so long as the review is confined to a determination as to whether the procedural requisites of NEPA have been followed." The court concluded that the ICC's decision not to suspend the surcharge for the seven-month period was a "major federal action significantly affecting the quality of the human environment," and granted an injunction prohibiting the ICC "from permitting" and the railroads "from collecting" the surcharge "insofar as that surcharge relates to goods being transported for purposes of recycling." *Held:*

1. Appellees' pleadings sufficiently alleged that they were "adversely affected" or "aggrieved" within the meaning of § 10 of the Administrative Procedure Act to withstand a motion to dismiss on the ground of lack of standing to sue. *Sierra Club* v. *Morton*, 405 U. S. 727, distinguished. Pp. 13–19.

(a) Standing is not confined to those who show economic harm, as "[a]esthetic and environmental well-being, like economic

well-being, are important ingredients of the quality of life in our society." *Sierra Club, supra,* at 734. P. 15.

(b) Here, the appellees claimed that the specific and allegedly illegal action of the ICC would directly harm them in their use of the natural resources of the Washington area. Pp. 15–16.

(c) Standing is not to be denied because many people suffer the same injury. Pp. 16–17.

(d) It cannot be said on these pleadings that appelles could not prove their allegations, which, if proved, would place them squarely among those persons injured in fact by the ICC's action and entitled to review under *Sierra Club, supra.* Pp. 17–19.

2. The District Court lacked jurisdiction to issue the injunction. Pp. 19–27.

(a) *Arrow Transportation, supra,* held that Congress in § 15 (7) had vested exclusive jurisdiction in the ICC to suspend rates pending its final decision on their lawfulness and had deliberately extinguished judicial power to grant such relief; and the factual distinctions between the instant case and *Arrow Transportation* are inconsequential. Pp. 19–21.

(b) The alleged noncompliance by the ICC with NEPA did not give the District Court authority to grant the injunction, as NEPA was not intended to repeal by implication any other statute, and the policies identified in *Arrow Transportation* as the basis for § 15 (7) would be substantially undermined if the courts were found to have suspension powers simply because of noncompliance with NEPA. Pp. 21–26.

346 F. Supp. 189, reversed and remanded.

STEWART, J., delivered the opinion of the Court, which BRENNAN and BLACKMUN, JJ., joined; in Parts I and II of which DOUGLAS and MARSHALL, JJ., joined; and in Parts I and III of which BURGER, C. J., and WHITE and REHNQUIST, JJ., joined. BLACKMUN, J., filed a concurring opinion, in which BRENNAN, J., joined. DOUGLAS, J., filed an opinion dissenting in part. WHITE, J., filed an opinion dissenting in part, in which BURGER, C. J., and REHNQUIST, J., joined. MARSHALL, J., filed an opinion concurring in part and dissenting in part. POWELL, J., took no part in the consideration or decision of the cases.

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SUPREME COURT OF THE UNITED STATES

Nos. 72–535 AND 72–562

United States and Interstate Commerce Commission, Appellants,
72–535 *v.*
Students Challenging Regulatory Agency Procedures (SCRAP) et al.

Aberdeen and Rockfish Railroad Company et al., Appellants,
72–562 *v.*
Students Challenging Regulatory Agency Procedures (SCRAP) et al.

On Appeals from the United States District Court for the District of Columbia.

[June 18, 1973]

MR. JUSTICE STEWART delivered the opinion of the Court.

Under the Interstate Commerce Act, the initiative for rate increases remains with the railroads. But in the absence of special permission from the Interstate Commerce Commission, a railroad seeking an increase must provide at least 30 days' notice to the Commission and the public before putting the new rate into effect. 49 U. S. C. § 6 (3).[1] During that 30-day period, the Com-

[1] 49 U. S. C. § 6 (3) provides: "No change shall be made in the rates, fares, and charges or joint rates, fares, and charges which have been filed and published by any common carrier in compliance with the requirements of this section, except after thirty days'

mission may suspend the operation of the proposed rate for a maximum of seven months pending an investigation and decision on the lawfulness of the new rates. 49 U. S. C. § 15 (7).[3] At the end of the seven-month

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notice to the Commission and to the public published as aforesaid, which shall plainly state the changes proposed to be made in the schedule then in force and the time when the changed rates, fares, or charges will go into effect; and the proposed changes shall be shown by printing new schedules, or shall be plainly indicated upon the schedules in force at the time and kept open to public inspection: *Provided*, That the Commission may, in its discretion and for good cause shown, allow changes upon less than the notice herein specified, or modify the requirements of this section in respect to publishing, posting, and filing of tariffs, either in particular instances or by a general order applicable to special or peculiar circumstances or conditions: *Provided further*, That the Commission is authorized to make suitable rules and regulations for the simplification of schedules of rates, fares, charges, and classifications and to permit in such rules and regulations the filing of an amendment of or change in any rate, fare, charge, or classification without filing complete schedules covering rates, fares, charges or classifications not changed if, in its judgment, not inconsistent with the public interest."

[3] 49 U. S. C. § 15 (7) provides in pertinent part: "Whenever there shall be filed with the Commission any schedule stating a new . . . rate, fare, or charge, . . . the Commission shall have . . . authority, either upon complaint or upon its own initiative without complaint, at once, and if it so orders without answer or other formal pleading by the interested carrier or carriers, but upon reasonable notice, to enter upon a hearing concerning the lawfulness of such rate, fare, [or] charge . . . ; and pending such hearing and the decision thereon the Commission, upon filing with such schedule and delivering to the carrier or carriers affected thereby a statement in writing of its reasons for such suspension, may from time to time suspend the operation of such schedule and defer the use of such rate, fare, [or] charge . . . , but not for a longer period than seven months beyond the time when it would otherwise go into effect; and after full hearing, whether completed before or after the rate, fare, [or] charge . . . goes into effect, the Commission may make such order with reference

period, the carrier may put the suspended rate into effect unless the Commission has earlier completed its investigation and found the rate unlawful.[2]

Proceeding under this regulatory scheme, on December 13, 1971, substantially all of the railroads in the United States requested Commission authorization to file on 5 days' notice a 2.5% surcharge on nearly all freight rates. The railroads sought a January 1, 1972 effective date for the new rates. The surcharge was proposed as an interim emergency measure designed to produce some $246 million annually in increased revenues pending adoption of selective rate increases on a permanent basis.

As justification for the proposed surcharge, the railroads alleged increasing costs and severely inadequate

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thereto as would be proper in a proceeding initiated after it had become effective. If the proceeding has not been concluded and an order made within the period of suspension, the proposed change of rate, fare, [or] charge . . . . shall go into effect at the end of such period; but in case of a proposed increased rate or charge for or in respect to the transportation of property, the Commission may by order require the interested carrier or carriers to keep accurate account in detail of all amounts received by reason of such increase, specifying by whom and in whose behalf such amounts are paid, and upon completion of the hearing and decision may by further order require the interested carrier or carriers to refund, with interest, to the persons in whose behalf such amounts were paid, such portion of such increased rates or charges as by its decision shall be found not justified. At any hearing involving a change in a rate, fare, [or] charge . . . after September 18, 1940, the burden of proof shall be upon the carrier to show that the proposed changed rate, fare, [or] charge . . . is just and reasonable, and the Commission shall give to the hearing and decision of such questions preference over all other questions pending before it and decide the same as speedily as possible."

[2] Other statutory provisions giving suspension powers to the Commission include 49 U. S. C. §§ 316 (g), 318 (c) (Motor Carrier Act); 49 U. S. C. § 907 (g), (i) (Water Carrier Act); 49 U. S. C. § 1006 (e) (Freight Forwarders Act).

revenues. In its last general revenue increase case, less than two years earlier, the Commission had found:

> "[T]he financial condition of the railroad industry as a whole, and the financial status of many individual carriers by rail, must be found to be at a dangerously low level. The precipitous decline in working capital and serious loss of liquidity has reduced many carriers to a truly marginal operation. This has been most clearly demonstrated by the recent bankruptcy application of the Penn Central. We think it undeniable that a number of other roads are approaching a similar financial crisis." *Ex parte Nos. 265/267, Increased Freight Rates, 1970 and 1971*, 339 I. C. C. 125, 173.

The railroads alleged that, since the close of that proceeding, their costs had increased by over $1 billion on an annual basis, including $305 million in increased wages, while economic indicators such as decreased working capital and increased debt obligations pointed towards an ever worsening financial condition.[4]

In an order dated December 21, 1971, the Commission acknowledged the need, particularly of some carriers, for increased revenues, but it concluded that five days' notice and a January 1, 1972, effective date "would preclude the public from effective participation." *Ex parte No. 281, Increased Freight Rates and Charges*, 340 I. C. C. 358, 361. The Commission authorized the railroads to refile the 2.5% surcharge with not less than 30 days' notice, and an effective date no earlier than February 5, 1972.

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[4] Figures reported to the Commission indicated that the net working capital of the Class I railroads for the 12 months ending September 30, 1971, was only $75.4 million, approximately $33.7 million less than the year-end 1970 figure. Long-term debt maturing within one year from September 30, 1971, was $43.6 million higher than on December 31, 1970. Equipment obligations at the end of 1970 were $4,448 million or almost twice the total in 1960.

On January 5, 1972, the railroads refiled the surcharge to become effective on February 5, 1972. Shippers, competing carriers, and other interested persons requested the Commission to suspend the tariff for the statutory seven-month period. Various environmnetal groups, including Students Challenging Regulatory Agency Procedures (SCRAP) and the Environmental Defense Fund (EDF), two of the appellees here, protested that failure to suspend the surcharge would cause their members "economic, recreational and aesthetic harm." Specifically, they claimed that the rate structure would discourage the use of "recyclable" materials, and promote the use of new raw materials that compete with scrap, thereby adversely affecting the environment by encouraging unwarranted mining, lumbering, and other extractive activities. The members of these environmental groups were allegedly forced to pay more for finished products, and their use of forests and streams was allegedly impaired because of unnecessary destruction of timber and extraction of raw materials, and the accumulation of otherwise recyclable solid and liquid waste materials. The railroads replied that since this was a general rate increase, recyclable materials would not be made any less competitive relative to other commodities, and that in the past general rate increases had not discouraged the movement of scrap materials.

The Commission issued an order on February 1, 1972, shortly before the surcharge would have automatically become effective. It recognized that "the railroads have a critical need for additional revenue from their interstate freight rates and charges to offset, in part, recently incurred increased operating costs," and announced its decision not to suspend the 2.5% surcharge for the seven-month statutory period.[5] In anticipation of the pro-

[5] The order of the ICC is unreported.

posed permanent selective increases to be filed by the railroads and to avoid further complication of the tariff rates, the Commission specified that its refusal to suspend was conditioned upon the carriers' setting an expiration date for the surcharge of no later than June 5, 1972.[6] The Commission ordered the investigation into the railroads' rates which had been instituted by its December 21 order to be held in abeyance until the carriers requested permission to file the indicated permanent rate increases on a selective basis. With respect to the appellees' environmental arguments, the Commission found that "the involved general increase will have no significant adverse effect on the movement of traffic by railway or on the quality of the human environment within the meaning of the [National] Environmental Policy Act of 1969."

The proposed permanent selective increases, averaging 4.1%, were subsequently filed with the Commission, and various parties again requested that these proposed rates also be suspended. By order served March 6, 1972, the Commission did not grant the railroads' request to have the selective increases go into effect on April 1, 1972, as they had requested, but it allowed the carriers to republish their rates to become effective on May 1, 1972, upon not less than 45-days notice to the public. The carriers did republish the rates, and on April 24, 1972, the Commission entered an order suspending the proposed selec-

[6] The Commission also imposed as a condition on its refusal to suspend the exclusion of increased rates "on freight in trailer bodies, semi-trailers, vehicles or containers on flat cars, on export and import traffic." Since such increases had been proposed only by the western and southern carriers and not by the eastern carriers, such increases would, in the Commission's view, have disrupted existing port relationships.

Finally, the Commission conditioned its action on the provision that the proposed surcharge would not apply to shipments originating prior to February 5, 1972, and moving under transit arrangements.

tive increase for the full seven-month period allowed by statute, or to and including November 30, 1972.[7] The investigation into the increased rates was continued. Since the selective increases were to supplant the temporary surcharge, and since they had been suspended, the Commission modified its February 1 order and authorized the railroads to eliminate the June 5 expiration date for the surcharge and to continue collecting the surcharge until November 30, 1972.

I

On May 12, 1972, SCRAP filed the present suit against the United States and the Commission in the District Court for the District of Columbia seeking, along with other relief, a preliminary injunction to restrain enforcement of the Commission's February 1 and April 24 orders allowing the railroads to collect the 2.5% surcharge.

SCRAP stated in its amended complaint that it was "an unincorporated association formed by five law students . . . in September, 1971. Its primary purpose is to enhance the quality of the human environment for its members and for all citizens . . . ." To establish standing to bring this suit, SCRAP repeated many of the allegations it had made before the Commission in *Ex parte 281*. It claimed that each of its members "suffered economic, recreational and aesthetic harm directly as a result of the adverse environmental impact of the railroad freight structure, as modified by the Commission's actions to date in *Ex Parte 281*." Specifically SCRAP alleged that each of its members was caused to pay more for finished products, that each of its members "uses the forests, rivers, streams, mountains, and other natural resources surrounding the Washington Metropolitan area and at his legal residence, for camping, hiking, fishing, sightseeing, and other recreational [and] aesthetic pur-

[7] The March 6 and April 24 orders of the ICC are unreported.

poses," and that these uses have been adversely affected by the increased freight rates, that each of its members breathes the air within the Washington Metropolitan Area and the area of his legal residence and that this air has suffered increased pollution caused by the modified rate structure, and that each member has been forced to pay increased taxes because of the sums which must be expended to dispose of otherwise reusable waste materials.

The main thrust of SCRAP's complaint was that the Commission's decisions of February 1 and April 24, insofar as they declined to suspend the 2.5% surcharge, were unlawful because the Commission had failed to include a detailed environmental impact statement as required by § 102 (C) of the National Environmental Policy Act of 1969 (NEPA), 42 U. S. C. § 4332 (C). NEPA requires such a statement in "every recommendation or report on proposals for legislation and other major Federal actions significantly affecting the quality of the human environment . . . ." *Ibid.*[8] SCRAP contended that because

[8] Section 102, 42 U. S. C. § 4332, provides in pertinent part:

"The Congress authorizes and directs that, to the fullest extent possible: (1) the policies, regulations, and public laws of the United States shall be interpreted and administered in accordance with the policies set forth in this chapter, and (2) all agencies of the Federal Government shall—

. . . . . .

"(C) include in every recommendation or report on proposals for legislation and other major Federal actions significantly affecting the quality of the human environment, a detailed statement by the responsible official on—

"(i) the environmental impact of the proposed action,

"(ii) any adverse environmental effects which cannot be avoided should the proposal be implemented,

"(iii) alternatives to the proposed action.

"(iv) the relationship between local short-term uses of man's environment and the maintenance and enhancement of long-term productivity, and

"(v) any irreversible and irretrievable commitments of resources

of its alleged adverse impact upon recycling, the Commission's action with respect to the surcharge constituted a major federal action significantly affecting the environment.

Three additional environmental groups, also appellees here, were allowed to intervene as plaintiffs, and a group of railroads, appellants here, intervened as defendants to support the 2.5% surcharge.[9] After a single district

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which would be involved in the proposed action should it be implemented.

"Prior to making any detailed statement, the responsible Federal official shall consult with and obtain the comments of any Federal agency which has jurisdiction by law or special expertise with respect to any environmental impact involved. Copies of such statement and the comments and views of the appropriate Federal, State, and local agencies, which are authorized to develop and enforce environmental standards, shall be made available to the President, the Council on Environmental Quality and to the public . . . and shall accompany the proposal through the existing agency review processes . . . ."

[9] The Environmental Defense Fund (EDF), National Parks and Conservation Association, and Izaak Walton League of America intervened as plaintiffs. The allegations as to standing made by each of these groups were similar to those made by SCRAP. EDF, for example, alleged as follows:

"EDF has a nationwide membership of over 32,000 persons composed of scientists, educators, lawyers and other citizens dedicated to the protection of our environment and the wise use of our natural resources. Each of EDF's members has a personal interest in the maintenance of a safe, healthful, productive environment as free from waste substances as is possible. EDF's members have contributed financially to EDF in part so that they may obtain adequate representation of their legally protected environmental interests, which representation they could not otherwise individually afford. Each of EDF's members has under § 101 (c) of NEPA, 'a responsibility to contribute to the preservation and enhancement of the environment,' which responsibility they fulfill in part by becoming a member of and contributing to EDF.

"The increased freight rates and charges in *Ex Parte 281* and the continuance of the underlying rate structure, which discriminate

judge had denied the defendants' motion to dismiss and SCRAP's motion for a temporary restraining order, a statutory three-judge district court was convened pursuant to 28 U. S. C. §§ 2325, 2284, to decide the motion for a preliminary injunction and the cross-motion to dismiss the complaint.

On July 10, 1972, the District Court filed an opinion, 346 F. Supp. 189, and entered an injunction forbidding the Commission "from permitting," and the railroads "from collecting" the 2.5% surcharge "insofar as that surcharge relates to goods being transported for purposes of recycling, pending further order of this court." [10]

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against movement of secondary (recyclable) materials, will cause EDF members individualized injury and adversely affect them in one or more of their activities and pastimes. Specifically, each EDF member: (i) has been or will be caused to pay more for products in the market place, made more expensive by both the non-use of recycled materials in their manufacture, and the need to use comparatively more energy in processing primary raw materials as opposed to secondary (recyclable) materials; (ii) uses the nation's forests, rivers, streams, mountains, and other natural resources for camping, hiking, fishing, sightseeing, and other recreational and aesthetic purposes. These uses have been and will continue to be adversely affected to the extent that the freight rate structure, as modified thus far in *Ex Parte 281*, encourages destruction of virgin timber, the unnecessary extraction of nonrenewable resources, and the discharge and accumulation of otherwise recyclable materials."

[10] The Court dismissed as moot that part of the complaint relating to the Commission's February 1 order because that order had expired by its own terms on June 5. Since the environmental groups have not appealed from the judgment below, we have before us for review only the District Court's action with regard to the Commission's April 24 order that allowed the surcharge to continue until November 30, 1972.

The Court also concluded that since the Commission had taken no final action with respect to the 4.1% selective increase, the lawfulness of that tariff was not ripe for review. The Court did, however, retain jurisdiction over the case to review the final order of the Commission.

The Court first rejected the contention that the appellees were without standing to sue because they allegedly had no more than "a general interest in seeing that the law is enforced," *id.*, at 195, and distinguished our recent decision in *Sierra Club* v. *Morton*, 405 U. S. 727, on the basis that, unlike the petitioner in *Sierra Club*, the environmental groups here had alleged that their members used the forests, streams, mountains and other resources in the Washington area and that this use was disturbed by the environmental impact caused by nonuse of recyclable goods.

Second, the Court found that its power to grant an injunction was not barred by our decision in *Arrow Transportation Co.* v. *Southern R. Co.*, 372 U. S. 658, 667, where we held that in enacting 49 U. S. C. § 15 (7), Congress had intentionally vested "in the Commission the sole and exclusive power to suspend and [withdrew] from the judiciary any pre-existing power to grant injunctive relief." The Court reasoned that NEPA "implicitly confers authority on the federal courts to enjoin *any* federal action taken in violation of NEPA's procedural requirements . . . so long as the review is confined to a determination as to whether the procedural requisites of NEPA have been followed." 346 F. Supp., at 197 and n. 11.

Finally, turning to the merits, the Court concluded that the Commission's April 24 decision not to suspend the surcharge for the statutory seven-month period was a "major Federal action significantly affecting the quality of the human environment." On the premise that an environmental impact statement is required "whenever the action *arguably* will have an adverse environmental impact," *id.*, at 201, the Court held that "the danger of an adverse impact is sufficiently real to require a statement in this case." *Ibid.*

The District Court declined to stay its injunctive order pending appeal to this Court, and on July 19, 1972, THE

CHIEF JUSTICE, as Circuit Justice for the District of Columbia Circuit, denied applications to stay the preliminary injunction. 409 U. S. 1207. On December 18, 1972, we noted probable jurisdiction of the appeals filed by the United States, the Commission, and the railroads. 409 U. S. 1073.[11]

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[11] While subsequent events do not bear directly on the validity of the District Court's action in granting the preliminary injunction, they do highlight the problems that hover in the background of this litigation.

On October 4, 1972, the Commission served its report and order in *Ex parte 281* approving, with some exceptions, the general increases filed by the railroads. *Increased Freight Rates and Charges, 1972*, 341 I. C. C. 290. In that report, although the Commission gave extensive consideration to environmental aspects of the rate increases, it declined to include a formal environmental impact statement because it concluded that its actions "will neither actually nor potentially significantly affect the quality of the human environment . . . ." *Id.*, at 314.

The selective increases were to become effective on October 23, 1972, but the Commission delayed until November 12, the effective date for rate increases on recyclable commodities in order to allow the submission of comments by interested parties. Upon the submission of critical comments, the Commission, in an unreported order served on November 8, reopened the rate proceeding in *Ex parte 281* for further evaluation of the rates on recyclable commodities, and ordered the proposed selective tariff increases on those commodities suspended for the full seven-month period authorized by statute—until June 10, 1973. Accordingly, with respect to recyclable commodities on which the proposed selective increase had been suspended, the Commission extended the expiration date of the 2.5% surcharge until June 10, 1973, the expiration date for the suspension of the selective increases. But the Commission acknowledged that the power to collect the surcharge on these recyclable commodities was barred by the preliminary injunction issued by the District Court in the present case and which is the subject of the present appeal. In short, the temporary 2.5% surcharge would have been in effect throughout this period on recyclable commodities but for the District Court's resilient preliminary injunction. Whether the Commission deliberately continued the surcharge beyond the time it would have been supplanted by the selective increases in order to

II

The appellants challenge the appellees' standing to sue, arguing that the allegations in the pleadings as to stand-

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give the surcharge and the District Court's injunction continuing effect and thus avoid mooting this case, and whether the Commission acted beyond its powers under 49 U. S. C. § 15 (7) by suspending the selective increases for a second seven-month period and by treating the District Court's injunction as having continuing effect, are questions not raised in this case. No party now maintains that this case is moot. Cf. *Southern Pacific Terminal Co.* v. *Interstate Commerce Commission*, 219 U. S. 498, 515.

Both sets of appellees filed motions in the District Court: SCRAP sought a preliminary injunction against the Commission's October 4 order, and EDF and the other intervening plaintiffs sought leave to file an amended and supplemental complaint and requested other relief. On January 9, 1973, the Court deferred consideration of the EDF motions and denied SCRAP's request for a preliminary injunction. The Court found that as a result of the Commission's November 8 order, neither the selective rate increases nor the temporary surcharge could be assessed on recyclable commodities. Consequently, the Court found, no injunctive relief was justified as to those materials. While the permanent rate increase approved by the Commission in *Ex parte 281* was then being collected on shipments of all other commodities, and although the Commission had concededly failed to file an impact statement, the Court concluded that "the danger of an adverse impact appears to be sufficiently speculative . . . that it would be unsound to grant preliminary relief." The Court continued: "The record indicates that many railroads are in dire financial straits—some on the verge of bankruptcy—and badly need the revenues now being obtained under the Commission's rate increase. The increase amounts to some $340 million per year, and were this revenue flow halted it could not easily be recouped should it later appear that no NEPA statement was necessary." The merits of neither the Commission's October 4 order nor the District Court's January 9 decision are before us, and we therefore express no opinion on them.

On May 7, 1973, the Commission served its final environmental impact statement relating to the selective rate increases on recyclable commodities. It concluded that the proposed increases would have no significant adverse effect on the environment. Contending that

ing were vague, unsubstantiated and insufficient under our recent decision in *Sierra Club* v. *Morton*, *supra*. The appellees respond that unlike the petitioner in *Sierra Club*, their pleadings sufficiently alleged that they were "adversely affected" or "aggrieved" within the meaning of § 10 of the Administrative Procedure Act (APA), 5 U. S. C. § 702,[12] and they point specifically to the allegations that their members used the forests, streams, mountains and other resources in the Washington Metropolitan Area for camping, hiking, fishing, and sightseeing, and that this use was disturbed by the adverse environmental impact caused by the nonuse of recyclable goods brought about by a rate increase on those commodities. The District Court found these allegations sufficient to withstand a motion to dismiss. We agree.

The petitioner in *Sierra Club*, "a large and long-established organization, with a historic commitment to the cause of protecting our Nation's natural heritage from man's depredations," 405 U. S., at 739, sought a declaratory judgment and an injunction to restrain federal officials from approving the creation of an extensive ski-resort development in the scenic Mineral King Valley of the Sequoia National Forest. The Sierra Club claimed standing to maintain its "public interest" lawsuit because it had "a special interest in the conservation and

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the impact statement was inadequate, EDF and SCRAP sought to enjoin collection of the selective rate increases. On June 7, 1973, the District Court temporarily enjoined the railroads from collecting the selective increases on recyclable commodities. On June 8, 1973, THE CHIEF JUSTICE, as Circuit Justice for the District of Columbia Circuit, stayed the District Court's injunction pending further order of this Court.

[12] Like the petitioner in *Sierra Club*, the appellees here base their standing to sue upon § 10 of the Administrative Procedure Act (APA), 5 U. S. C. § 702, which provides:

"A person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action within the meaning of a relevant statute, is entitled to judicial review thereof."

the sound maintenance of the national parks, game refuges and forests of the country. . . ." *Id.*, at 730. We held those allegations insufficient.

Relying upon our prior decisions in *Data Processing Services* v. *Camp*, 397 U. S. 150, and *Barlow* v. *Collins*, 397 U. S. 159, we held that § 10 of the APA conferred standing to obtain judicial review of agency action only upon those who could show "that the challenged action had caused them 'injury in fact,' and where the alleged injury was to an interest 'arguably within the zone of interests to be protected or regulated' by the statutes that the agencies were claimed to have violated." 405 U. S., at 733.[13]

In interpreting "injury in fact" we made it clear that standing was not confined to those who could show "economic harm," although both *Data Processing* and *Barlow* had involved that kind of injury. Nor, we said, could the fact that many persons shared the same injury be sufficient reason to disqualify from seeking review of an agency's action any person who had in fact suffered injury. Rather, we explained: "Aesthetic and environmental well-being, like economic well-being, are important ingredients of the quality of life in our society, and the fact that particular environmental interests are shared by the many rather than the few does not make them less deserving of legal protection through the judicial process." *Id.*, at 734. Consequently, neither the fact that the appellees here claimed only a harm to their use and enjoyment of the natural resources of the Wash-

[13] As in *Sierra Club*, it is unnecessary to reach any question concerning the scope of the "zone of interests" test or its application to this case. It is undisputed that the "environmental interest" that the appellees seek to protect is within the interests to be protected by NEPA, and it is unnecessary to consider the various allegations of economic harm on which the appellees also relied in their pleadings and which the Government contends are outside the intended purposes of NEPA.

ington area, nor the fact that all those who use those resources suffered the same harm, deprives them of standing.

In *Sierra Club*, though, we went on to stress the importance of demonstrating that the party seeking review be himself among the injured, for it is this requirement that gives a litigant a direct stake in the controversy and prevents the judicial process from becoming no more than a vehicle for the vindication of the value interests of concerned bystanders. No such specific injury was alleged in *Sierra Club*. In that case the asserted harm "will be felt directly only by those who use Mineral King and Sequoia National Park, and for whom the aesthetic and recreational values of the area will be lessened by the highway and ski resort," *id.*, at 735, yet "[t]he Sierra Club failed to allege that it or its members would be affected in any of their activities or pastimes by the . . . development." *Ibid.* Here, by contrast, the appellees claimed that the specific and allegedly illegal action of the Commission would directly harm them in their use of the natural resources of the Washington Metropolitan Area.

Unlike the specific and geographically limited federal action of which the petitioner complained in *Sierra Club*, the challenged agency action in this case is applicable to substantially all of the Nation's railroads, and thus allegedly has an adverse environmental impact on all the natural resources of the country. Rather than a limited group of persons who used a picturesque valley in California, all persons who utilize the scenic resources of the country, and indeed all who breathe its air, could claim harm similar to that alleged by the environmental groups here. But we have already made it clear that standing is not to be denied simply because many people suffer the same injury. Indeed some of the cases on which we relied in *Sierra Club* demonstrated the patent fact that persons

across the Nation could be adversely affected by major governmental actions. See, *e. g., Environmental Defense Fund* v. *Hardin,* 428 F. 2d 1093, 1097 (interests of consumers affected by decision of Secretary of Agriculture refusing to suspend registration of certain pesticides containing DDT); *Reade* v. *Ewing,* 205 F. 2d 630, 631–632 (interests of consumers of oleomargarine in fair labeling of product regulated by Federal Security Administration). To deny standing to persons who are in fact injured simply because many others are also injured, would mean that the most injurious and widespread Government actions could be questioned by nobody. We cannot accept that conclusion.

But the injury alleged here is also very different from that at issue in *Sierra Club* because here the alleged injury to the environment is far less direct and perceptible. The petitioner there complained about the construction of a specific project that would directly affect the Mineral King Valley. Here, the Court was asked to follow a far more attenuated line of causation to the eventual injury of which the appellees complained—a general rate increase would allegedly cause increased use of nonrecyclable commodities as compared to recyclable goods, thus resulting in the need to use more natural resources to produce such goods, some of which resources might be taken from the Washington area, and resulting in more refuse that might be discarded in national parks in the Washington area. The railroads protest that the appellees could never prove that a general increase in rates would have this effect, and they contend that these allegations were a ploy to avoid the need to show some injury in fact.

Of course, pleadings must be something more than an ingenious academic exercise in the conceivable. A plaintiff must allege that he has been or will in fact be perceptibly harmed by the challenged agency action.

not that he can imagine circumstances in which he could be affected by the agency's action. And it is equally clear that the allegations must be true and capable of proof at trial. But we deal here simply with the pleadings in which the appellees alleged a specific and perceptible harm that distinguished them from other citizens who had not used the natural resources that were claimed to be affected.[14] If, as the railroads now assert, these allegations were in fact untrue, then the appellants should have moved for summary judgment on the standing issue and demonstrated to the District Court that the allegations were sham and raised no genuine issue of fact.[15] We cannot say on these pleadings that the ap-

[14] The Government urges us to limit standing to those who have been "significantly" affected by agency action. But, even if we could begin to define what such a test would mean, we think it fundamentally misconceived. "Injury in fact" reflects the statutory requirement that a person be "adversely affected" or "aggrieved," and it serves to distinguish a person with a direct stake in the outcome of a litigation—even though small—from a person with a mere interest in the problem. We have allowed important interests to be vindicated by plaintiffs with no more at stake in the outcome of an action than a fraction of a vote, see *Baker* v. *Carr*, 369 U. S. 186; a five dollar fine and costs, see *McGowan* v. *Maryland*, 366 U. S. 420; and a $1.50 poll tax, *Harper* v. *Virginia Bd. of Elections*, 383 U. S. 663. While these cases were not dealing specifically with § 10 of the APA, we see no reason to adopt a more restrictive interpretation of "adversely affected" or "aggrieved." As Professor Davis has put it: "The basic idea that comes out in numerous cases is that an identifiable trifle is enough for standing to fight out a question of principle; the trifle is the basis for standing and the principle supplies the motivation." Davis, Standing: Taxpayers and Others, 35 U. Chi. L. Rev. 601, 613. See also K. Davis, Administrative Law Treatise, §§ 22.09–5 to 22.09–6 (1970 Supplement).

[15] The railroads object to the fact that the allegations were not more precise—that no specific "forest" was named, that there was no assertion of the existence of any lumbering camp or other extractive facility in the area. They claim that they had no way to answer such allegations which were wholly barren of specifics. But, if that

pellees could not prove their allegations which, if proved, would place them squarely among those persons injured in fact by the Commission's action, and entitled under the clear import of *Sierra Club* to seek review. The District Court was correct in denying the appellants' motion to dismiss the complaint for failure to allege sufficient standing to bring this lawsuit.

III

We need not reach the issue whether, under conventional standards of equity, the District Court was justified in issuing a preliminary injunction, because we have concluded that the Court lacked jurisdiction to enter an injunction in any event.

The District Court enjoined the Commission from "permitting," and the railroads from "collecting," the 2.5% interim surcharge on recyclable commodities. Finding that NEPA implicitly conferred authority "on the federal courts to enjoin *any* federal action taken in violation of NEPA's procedural requirements," 346 F. Supp., at 197, it concluded that our decision in *Arrow Transportation Co.* v. *Southern R. Co., supra,* did not affect judicial power to issue an injunction in the circumstances of this case. We cannot agree.

In *Arrow,* the Commission had suspended a railroad's proposed rates for the statutory seven-month period, and the railroad had voluntarily deferred the proposed rate

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were really a problem, the railroads could have moved for a more definite statement, see Rule 12 (e), Fed. Rule Civ. Proc., and certainly normal civil discovery devices were available to the railroads.

Similarly, the District Court cannot be faulted for failing to take evidence on the issue of standing. This case came before the Court on motions to dismiss and for a preliminary injunction. If the railroads thought that it was necessary to take evidence, or if they believed summary judgment was appropriate, they could have moved for such relief.

for an additional five months. When the Commission had not reached a final decision within that period, the railroad announced its intent to adopt the new rates. In a suit brought to enjoin the railroad from effectuating that change, we held that the courts were without power to issue such an injunction. From the language and history of § 15 (7) of the Interstate Commerce Act, we concluded that Congress had vested exclusive power in the Commission to suspend rates pending its final decision on their lawfulness, and had deliberately extinguished judicial power to grant such relief. The factual distinctions between the present case and *Arrow* are inconsequential.

It is true that the injunction in *Arrow* was sought after the statutory seven-month period had expired and thus represented an attempt to extend judicially the suspension period, while here the injunction was issued during the suspension period. But *Arrow* was grounded on the lack of power in the courts to grant any injunction before the Commission had finally determined the lawfulness of the rates, and that holding did not depend on the fact that the availability of the Commission's power of suspension had passed. Indeed, the federal court decisions cited and approved in *Arrow* involved instances where the courts had been asked to enjoin rates *during* the statutory seven-month period. See, *e. g.*, *M. C. Kiser Co.* v. *Central of Georgia R. Co.*, 236 F. 573, aff'd, 239 F. 718; *Freeport Sulphur Co.* v. *United States*, 199 F. Supp. 913; *Bison S. S. Corp.* v. *United States*, 182 F. Supp. 63; *Luckenbach S. S. Co.* v. *United States*, 179 F. Supp. 605, 609–610, vacated in part as moot, 364 U. S. 280; *Carlsen* v. *United States*, 107 F. Supp. 398.

Similarly, there is no significance in the fact that, unlike *Arrow*, the injunction in this case ran against

the Commission as well as the railroads. The only way in which the Commission could comply with the Court's order would be to exercise its power of suspension and suspend the surcharge. The injunction constitutes a direct interference with the Commission's discretionary decision whether or not to suspend the rates. It would turn *Arrow* into a sheer formality and effectively amend § 15 (7) if a federal court could accomplish by injunction against the Commission what it could not accomplish by injunction directly against the railroads. And again, the federal court decisions on which *Arrow* relied were for the most part cases in which the courts had held that they were without power to compel the Commission to grant a rate suspension. See, *e. g.*, *Bison S. S. Corp.* v. *United States, supra; Luckenbach S. S. Co.* v. *United States, supra; Carlsen* v. *United States, supra;* cf. *Freeport Sulphur Co.* v. *United States, supra.*[16]

Thus the only arguably significant distinction between the present case and *Arrow* is that here the Commission allegedly failed to comply with NEPA. However, we cannot agree with the District Court that NEPA has amended § 15 (7) *sub silentio* and created an implicit

[16] EDF suggests that the April 24 order of the Commission was in fact a final order finding the surcharge "just and reasonable," not simply a refusal to suspend the surcharge. But the Commission's reference to the "just and reasonable" nature of the surcharge was a preliminary assessment commonly made in suspension orders. See, *e. g.*, the suspension orders quoted in *Naph-Sol Refining Co.* v. *United States*, 269 F. Supp. 530, 531; *Oscar Mayer & Co.* v. *United States*, 268 F. Supp. 977, 978–979. It did not represent a final determination by the Commission that any particular rate was just and reasonable. Indeed the Commission made it clear in its February 1 order that the surcharge was not considered a prescribed rate within the meaning of *Arizona Grocery Co.* v. *Atchison, T. & S. F. R. Co.*, 284 U. S. 370, and was subject to complaint and investigation under the Act.

exception to *Arrow* so that judicial power to grant injunctive relief in this case has been revived.[17] NEPA, one of the recent major federal efforts at reversing the deterioration of the country's environment, declares "that it is the continuing policy of the Federal Government . . . to use all practicable means and measures . . . in a manner calculated to foster and promote the general welfare, to create and maintain conditions under which man and nature can exist in productive harmony, and fulfill the social, economic, and other requirements of present and future generations of Americans." 42 U. S. C. § 4331. To implement these lofty purposes, Congress imposed a number of responsibilities upon federal agencies, most notably the requirement of producing a detailed environmental impact statement for "major Federal actions significantly affecting the quality of the

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[17] An alternative ground for avoiding the *Arrow* decision, which was suggested but not relied on by the District Court, was that the surcharge here was an "agency-made" rate, not a "carrier-made" rate. *Moss* v. *CAB*, 430 F. 2d 891, which was cited by the Court is, however, plainly inapposite. There the CAB suspended the rates proposed by the carriers, but suggested in their place "a complete and innovative scheme for setting all passenger rates for the United States." *Id.*, at 899. It was clear that when the carriers filed the rates suggested by the Board they would not be suspended. "Even a cursory reading of the order makes it clear that the Board told the carriers what rates to file, it set forth a step-by-step formula requiring major changes in rate-making practices and in rates which it expected the carriers to adopt." *Id.*, at 899–900. Here, by contrast, the level and structure of the rates were proposed entirely by the carriers. While the Commission suggested an expiration date for the surcharge, this was simply to make the surcharge expire when the general selective increases went into effect. This expiration date and the other standard conditions attached to the Commission's refusal to suspend the surcharge did not, in any meaningful sense, transform the carrier-made rate into a Commission-made rate.

human environment." 42 U. S. C. § 4332 (C).[18] But nowhere, either in the legislative history or the statutory language, is there any indication that Congress intended to restore to the federal courts the power temporarily to suspend railroad rates, a power that had been clearly taken away by § 15 (7) of the Interstate Commerce Act.

The statutory language in fact indicates that NEPA was not intended to repeal by implication any other statute. Thus, 42 U. S. C. § 4335 specifies that "The policies and goals set forth in [NEPA] are supplementary to those set forth in existing authorizations of Federal agencies," and 42 U. S. C. § 4334 instructs that the Act "shall [not] in any way affect the specific statutory obligations of any Federal agency . . . ." Rather than providing for any wholesale overruling of prior law, NEPA requires all federal agencies to review their "present statutory authority, administrative regulations, and current policies and procedures for the purpose of determining whether there are any deficiencies or inconsistencies therein which prohibit full compliance with the purposes and provisions of [NEPA] and shall propose to the President . . . such measures as may be necessary to bring their authority and policies into conformity with the intent, purposes, and procedures set forth in [NEPA]." 42 U. S. C. § 4333. It would be anomalous if Congress had provided at one and the same time that federal agencies, which have the primary responsibility for the implementation of NEPA,[19] must comply with present law and ask for any necessary new

[18] See n. 8, *supra*.

[19] See *Greene County Planning Board* v. *FPC*, 455 F. 2d 412, 420; *Calvert Cliffs' Coordinating Comm'n* v. *United States Atomic Energy Comm'n*, 449 F. 2d 1109, 1119; *City of New York* v. *United States*, 337 F. Supp. 150, 160; *Cohen* v. *Price Comm'n*, 337 F. Supp. 1236, 1241.

legislation, but that the courts may simply ignore what we described in *Arrow* as "a clear congressional purpose to oust judicial power . . . ." 372 U. S., at 671 n. 22.[20]

The District Court pointed to nothing either in the language or history of NEPA that suggests a restoration of previously eliminated judicial power. While it relied primarily on the decisions of the Court of Appeals for the District of Columbia Circuit in *Calvert Cliffs' Coordinating Comm'n* v. *United States Atomic Energy Comm'n*, 449 F. 2d 1109, and *Committee for Nuclear Responsibility, Inc.* v. *Seaborg*, 463 F. 2d 783, neither case supports an injunction under the circumstances of this case. *Calvert Cliffs* held that a federal court had power to review rules promulgated by the Atomic Energy Commission, and there the court ordered further consideration of the rules on the ground that there had not been compliance with NEPA. In *Committee for Nuclear Responsibility* it was held that federal courts had jurisdiction to consider whether an executive decision to conduct a nuclear test had satisfied the procedural requirements of NEPA. The question here, however, is

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[20] The argument that NEPA implicitly restored to the courts the injunctive power that § 15 (7) had divested is similar to a contention rejected in *Arrow* itself. There the petitioners claimed that congressional adoption of the National Transportation Policy, 54 Stat. 899, had implicitly altered § 15 (7). They claimed that the proposed new railroad rates would drive the barge lines out of existence, contrary to the congressional declaration of concern for the protection of water carriers threatened by rail competition. The Court concluded that "nothing in the National Transportation Policy, enacted many years after . . . § 15 (7), indicates that Congress intended to revive a judicial power which . . . was extinguished when the suspension power was vested in the Commission." 372 U. S., at 673. In addition, the Court noted that, as is also true with NEPA, the mandate was directed not to the Courts but to the Commission. There is nothing about NEPA that makes it any more amenable for finding an implicit amendment of § 15 (7), than the National Transportation Policy was.

not whether there is general judicial power to determine if an agency has complied with NEPA, and to grant equitable relief if it has not, cf. *Arrow Transportation Co.* v. *Southern R. Co., supra,* at 671 n. 22; *Scripps Howard Radio Inc.* v. *FCC,* 316 U. S. 4, but rather whether in a specific context NEPA *sub silentio* revived judicial power that had been explicitly eliminated by Congress. *Calvert Cliffs'* and *Committee for Nuclear Responsibility* have nothing to say on this issue, for neither was concerned with a specific statute that restricts the power of the federal courts to grant injunctions.[21]

Our conclusion that the District Court lacked the power to grant the present injunction is confirmed by the fact that each of the policies that we identified in *Arrow* as the basis for § 15 (7) would be substantially undermined if the courts were found to have suspension powers simply because noncompliance with NEPA was alleged.

First, *Arrow* found that the Commission had been granted exclusive suspension powers in order to avoid the diverse results that had previously been reached by the courts. District courts had differed as to the existence and scope of any power to grant interim relief, with the consquence that the uniformity of rates had been jeopardized, and different shippers, carriers, and areas of the country had been subjected to disparate treatment. Similarly, since a suit to enjoin a national rate increase on NEPA grounds could be brought in any federal district court in the country, see 28 U. S. C. §§ 2284, 2321–2325, the result might easily be that the courts would "[reach] diverse results, . . . [engendering] confusion

[21] Indeed *Calvert Cliffs'* indicated that the requirements of § 102 of NEPA, see n. 8, *supra,* did not have to be complied with, if such compliance was precluded by another statutory provision. 449 F. 2d, at 1115. And *Committee for Nuclear Responsibility,* in another context, endorsed a principle, equally applicable here, that "repeal by implication is disfavored." 463 F. 2d, at 785.

and [producing] competitive inequities." 372 U. S., at 663. In short, a rate increase allowed in New York might be disallowed in New Jersey.

Second, we stressed in *Arrow* that § 15 (7) represents a careful accommodation of the various interests involved. The suspension period was limited as to time to prevent excessive harm to the carriers, for the revenues lost during that period could not be recouped from the shippers. On the other hand, Congress was aware that if the Commission did not act within the suspension period, then the new rates would automatically go into effect and the shippers would have to pay increased rates that might eventually be found unlawful. To mitigate this loss, Congress authorized the Commission to require the carriers to keep detailed accounts and eventually to repay the increased rates if found unlawful. To allow judicial suspension for noncompliance with NEPA, would disturb this careful balance of interests. A railroad may depend for its very finanical life on an increased rate, and the rate may be perfectly just and reasonable. Granting an injunction against that rate based on the Commission's alleged noncompliance with NEPA, although the Commission had determined not to suspend the rate, would deprive the railroads of vitally needed revenues and result in an unjustified windfall to shippers.

Finally, we found in *Arrow* that any survival of a judicial power to grant interim injunctive relief would represent an undesirable interference with the orderly exercise of the Commission's power of suspension. Similarly, to grant an injunction in the present context, even though not based upon a substantive consideration of the rates, would directly interfere with the Commission's decision as to *when* the rates were to go into effect, and would ignore our conclusion in *Arrow* that "Congress meant to foreclose a judicial power to interfere

with the *timing* of rate changes which would be out of harmony with the uniformity of rate *levels* fostered by the doctrine of primary jurisdiction." *Id.*, at 668. As the Court of Appeals for the Second Circuit explained in *Port of New York Authority* v. *United States*, 451 F. 2d 783, 788, where, on the basis of alleged noncompliance with NEPA, an injunction was sought against a Commission order refusing to suspend rates:

> "The basis of the decision in *Arrow*—that to permit judicial interference with the Commission's suspension procedures would invite the very disruption in the orderly review of the lawfulness of proposed tariffs that Congress meant to preclude—applies with equal force to the issue now before us."

Accordingly, because the District Court granted a preliminary injunction suspending railroad rates when it lacked the power to do so,[22] its judgment must be re-

[22] In view of our conclusion that there was no power to grant the preliminary injunction, it is unnecessary for us to reach the other questions posed by the parties. For example, the Government and the railroads urge that, because of the pressures of time, an environmental impact statement is not required at the suspension stage of a rate proceeding, and, in any event, a decision by the Commission whether or not to suspend rates is not subject to judicial review. See *Port of New York Authority*, 451 F. 2d 783; *Oscar Mayer & Co.* v. *United States*, 268 F. Supp. 977; *M. C. Kiser Co.* v. *Central of Georgia R. Co.*, *supra*; *Freeport Sulphur Co.* v. *United States*, *supra*; *Luckenbach S. S. Co.* v. *United States*, *supra*; *Carlsen* v. *United States*, *supra*. The appellees in turn contend that some compliance with NEPA is possible at the suspension stage, and that such compliance is required if the statute is to be enforced "to the fullest extent possible." See 42 U. S. C. § 4332. And they urge that there is or should be an exception to the general principle of nonreviewability of suspension decisions for those cases where the Commission has acted beyond its statutory authority, or in violation of a clear statutory command or a procedural require-

versed and the case remanded to that court for further proceedings consistent with this opinion.

It is so ordered.

MR. JUSTICE POWELL took no part in the consideration or decision of these cases.

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ment, a standard that the appellees view as broad enough to encompass alleged noncompliance with NEPA. See *Naph-Sol Refining Co.* v. *United States*, 269 F. Supp. 530, 532; *Oscar Mayer & Co.* v. *United States*, *supra*, at 982 (Doyle, J., concurring); *Long Island R. Co.* v. *United States*, 193 F. Supp. 795. We express no view on any of these issues.

SUPREME COURT OF THE UNITED STATES

Nos. 72–535 AND 72–562

United States and Interstate Commerce Commission, Appellants, 72–535 *v.* Students Challenging Regulatory Agency Procedures (SCRAP) et al. Aberdeen and Rockfish Railroad Company et al., Appellants, 72–562 *v.* Students Challenging Regulatory Agency Procedures (SCRAP) et al.	On Appeals from the United States District Court for the District of Columbia.

[June 18, 1973]

MR. JUSTICE BLACKMUN, with whom MR. JUSTICE BRENNAN joins, concurring.

I join the Court's judgment and its opinion, but because of the presence of the first sentence of Part III of the opinion, and to avoid any misunderstanding as to my posture, I add a few words.

For the reasons stated in my dissenting opinion in *Sierra Club* v. *Morton*, 405 U. S. 727, 755 (1972), I would hold that the appellees here have standing to maintain this action based on their allegations of harm to the environment resulting from the Commission's order of April 24, 1972. And in evaluating whether injunctive relief is warranted, I would not require that the appellees, in their individual capacities, prove that they

in fact were injured. Rather, I would require only that appellees, as responsible and sincere representatives of environmental interests, show that the environment would be injured in fact and that such injury would be irreparable and substantial.

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[June 18, 1973]

MR. JUSTICE DOUGLAS, dissenting in part.

I

These cases present important environmental problems. They concern ratemaking for the shipment of litter for recycling. Paper, glass, and metals are the main items in today's garbage.[1] As indicated by the Bureau of Mines in Appendix I to this dissent, America's

[1] In a Bureau of Mines' survey, it was established that metals and glass account for approximately 75 weight-percent of the residues in municipal incinerator waste. Economics of Recycling Metals and Minerals from Urban Refuse, Bureau of Mines Technical Progress Report, April 1971, p. 2. From these materials, if recycled, familiar products such as bottles, newspapers, iron ingots, paper pulp, fuel oil, and methane gas can be manufactured. In addition, new products are being developed, such as glassphalt for street paving, insulation, glass wool, and glass bricks, in various colors that meet specifica-

method of disposing of garbage is either to use it for landfill or to put it first through incinerators and then to bury the residue. Sorting and recycling have several environmental impacts: (1) reduction in the use of incinerators lessens air pollution; (2) establishing or encouraging removal of litter from the landscape; (3) recycling saves both renewable and nonrenewable resources. As respects the last, the tons of paper that are recycled, rather than burned, can be translated into the number of standing trees that need not be cut for pulp the next year; the metals recycled protect our remaining nonrenewable supplies of ore, and so on.

Rates fixed so as to encourage vast shipments of litter are, therefore, perhaps the most immediate and dramatic illustration of a policy which will encourage protection of the environment against several erosive conditions.[2]

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tions for "severe weather"-facing-brick. Economics of Recycling Metals and Minerals from Urban Refuse, *supra*, p. 7.

This project was launched under the Resource Recovery Act of 1970, 84 Stat. 1227, 42 U. S. C. § 3251 *et seq.*, under which the Secretary of HEW was authorized to provide technical and financial assistance in planning and developing resource recovery and solid waste disposal programs.

For a detailed account of a Resource Recovery Mill see Ross, How to Succeed in Recycling. Environmental Quality Magazine, June 1973, p. 51.

[2] The necessity of reasonable trasportation rates is even more apparent when it is realized that the volume of residue which is processed at a major recycling plant is between 250 and 1,000 tons per day. (Economics of Recycling Metals and Minerals from Urban Refuse, Bureau of Mines Technical Progress Report, April 1971, p. 1.) Massive bulk transportation is therefore essential to these plant operations.

The problem is even more critical in urban areas where there is a high concentration of solid waste being generated and transportation to outlying recycling plants is a major cost factor. In 1968 a national survey found that an average of 8.2 pounds of waste per capita were collected daily in urban areas; this figure has now risen to 9 pounds. If present trends continue, this figure could be as high as 12 pounds in another 10 years. In our urban areas as a whole,

I would, therefore, affirm the eminently responsible decision of the District Court. 346 F. Supp. 189.

The Environmental Protection Act of 1969, 83 Stat. 856, 42 U. S. C. § 4321 *et seq.*, declares a congressional policy:

> ". . . which will encourage productive and enjoyable harmony between man and his environment; to promote efforts which will prevent or eliminate damage to the environment and biosphere and stimulate the health and welfare of man; to enrich the understanding of the ecological systems and natural resources important to the Nation; and to establish a Council on Environmental Quality."

That broad policy is further expounded in § 4331 (b) to include *inter alia*, the objective that "the nation may . . . (2) assure for all Americans safe, healthful, productive, and esthetically and culturally pleasing surroundings . . . and (6) enhance the quality of renewable resources and depletable services."

The Government urges that the petitioners do not have standing to challenge the administrative determination of railroad freight rate increases. SCRAP alleged in its amended complaint that its members suffered environmental and economic injury as a result of the alleged increase, because the increase diminished the total amount of waste recycling in the United States, and made those products, which were in fact manufactured from the waste materials after the rate increase, more expensive in the marketplace. In addition, SCRAP alleged that each of its members in fact use the "forests, rivers, streams, mountains, and other natural resources . . ." for recreational purposes, and these uses were adversely affected because the Commission's rate increases discourage the

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the solid waste generated is fast approaching a ton a year for each man, woman, and child. Science and Public Affairs, Energy Conservation and Waste Recycling, April 1973, p. 13, 17.

reuse of recyclable commodities, such as bottles and cans, and encourage the depletion of natural resources.

In *Sierra Club* v. *Morton*, 405 U. S. 727, 734, this Court stated that, "We do not question that [environmental] harm may amount to an 'injury in fact' sufficient to lay the basis for standing under § 10 of the APA. Aesthetic and environmental well-being, like economic well-being, are important ingredients of the quality of life in our society, and the fact that particular environmental interests are shared by the many rather than the few does not make them less deserving of legal protection through the judicial process." The members of SCRAP, have clearly alleged an "injury in fact" to the environment and to their own personal continued use of it.

"There is nothing unusual or novel in granting the consuming public standing to challenge administrative actions." (*Office of Communication of United Church of Christ* v. *FCC*, — U. S. App. D. C.—, 359 F. 2d 994.) This Court has indicated that where "statutes are concerned, the trend is toward enlargement of the class of people who may protest administrative action." (*Data Processing Service* v. *Camp*, 397 U. S. 150, 154.)

Littering is a commonplace phenomenon that affects every person, almost everywhere. By reports and writings we know that littering defaces mountain trails, alpine meadows, and even our highest peaks. Those in the valleys are often almost inundated with litter. Where a river is polluted and a person is dependent on it for drinking water, I suppose there would not be the slightest doubt that he would have standing in court to present his claim. I also suppose there is not the slightest doubt that where smog settles on a city, any person who must breathe that air or feel the sulphuric acid forming in his eyes, would have standing in court to present his claim. I think it is equally obvious that any resident

of an area whose paths are strewn with litter, whose parks, or picnic grounds are defaced by it has standing to tender his complaint to the Court. *Sierra Club* v. *Morton, supra,* would seem to cover this case, for littering abetted by the failure to recycle would clearly seem to implicate residents to whom "the aesthetic and recreational vaues of the area" are important. *Id.,* at 735. For the reasons stated in my opinion in *Sierra Club* v. *Morton, supra,* I agree with the Court that appellees have standing, but like MR. JUSTICE BLACKMUN, I would not require appellees, in their individual capacity, to prove injury in fact. As MR. JUSTICE BLACKMUN states, it should be sufficient if appellees, "as responsible and sincere representatives of environmental interests, show that the environment would be injured in fact. . . ."

II

The Council on Environmental Quality (CEQ), created in the executive office of the President, 42 U. S. C. § 4342, estimated in 1969 that this Nation produced more than 4.3 billion tons of solid refuse, including about 30 million tons of paper, 30 million tons of industrial fly ash, 15 million tons of scrap metal, 4 million tons of plastics, 100 million automobile tires, 30 billion bottles, 60 billion cans, and millions of discarded automobiles and appliances. First Annual Report of CEQ, Aug. 1970, pp. 107–113. It reported that while most of the secondary material could be reused as a replacement for virgin material, only a small fraction was recycled. *Ibid.* One of the reasons for the absence of recycling was the high cost both of collection of the material and the transportation costs. *Ibid.*

As noted, one of the purposes of the Act was to "enhance the quality of renewable resources and approach the maximum attainable recycling of depletable re-

sources." 42 U. S. C. § 4331 (b)(6). On October 9, 1970, Chairman Russell Train of CEQ wrote the Interstate Commerce Commission as follows:

> "The Council on Environmental Quality is deeply concerned with all facets of environmental quality. Solid waste disposal is one important aspect of the total pollution problem, and recycling is a new and desirable alternative to solid waste disposal which the Council strongly supports. The degree to which this technique will be used depends almost entirely on economics. Transportation costs, to the degree they increase secondary or scrap materials costs compared to the raw materials with which they compete, act as a disincentive to recycling. The Council believes that several rail haul costs biases currently exist and would like to discuss these cases with you. . . . In general, across-the-board percentage increases only widen existing price biases against secondary materials. Also, these increases raise the costs of doing business which can hinder the salvage and reclamation industry. In light of the President's concern with environmental quality, the growing problems of solid waste and the importance of recycling to alleviating them, I would like to express the Council's hope that the Interstate Commerce Commission's actions on the key issue of scrap material transportation rates will be consistent with the Nation's environmental quality goals."

In December 1971 substantially all the railroads filed with the Commission a request to impose a 2.5% surcharge on virtually all freight. The procedural details which followed are not presently material. Suffice it to say that shippers of recyclable materials submitted verified statements in support of their view that rate increases

would intensify the disincentives to shipment and use of recyclable materials. Thus the Institute for Scrap Iron and Steel submitted a study showing:

> "(1) Present scrap markets are retarded because of transport rates which encourage the usage of iron ore. (2) Future scrap markets are being affected because new investment that would logically be directed to scrap-intensive steelmaking is diverted because of the existing freight rate structure to ore-intensive steelmaking. (3) Iron ore (a limited domestic natural resource) is being exploited when it can and should be conserved. (4) Some scrap iron that should be recycled is unable to move, thus the environment is despoiled by unnecessary accumulations of solid metallic waste."

The Commission instituted a proceeding concerning the guidelines which environmental impact statements required under the Act should follow. 339 I. C. C. 508. A spokesman for the eastern roads filed an impact statement which said that "any possible adverse environmental impact in the form of reduced movements of commodities by rail will come only if we fail to provide adequate and efficient service" and that the need of the railroads to that end was for increased revenues. Appellees filed a protest and a request for a suspension of the proposed surcharge alleging that the present railroad rate structure discourages the movement of "recyclable" goods and that the surcharge would further discourage recycling.

The Commission, allowing the surcharge for a limited period, found that it would "have no significant adverse effect in the movement of traffic by railway or on the quality of the human environment" within the meaning of the 1969 Act. 340 I. C. C. 358; 341 I. C. C. 287.

Chairman Train of CEQ protested to the Commission:

"It is understandable that difficulties will be encountered in quantifying the environmental consequences of an incremental freight rate increase on recyclable materials. In our view, however, these consequences must be assessed in the light of the rate disparity between secondary and primary materials that gives rise to the problem in the first place. This disparity is a matter of an entirely different magnitude, calling for a thorough environmental assessment as a precondition to determining whether subsequent incremental increases require additional environmental impact statements. . . . Clearly at some point increases which might be individually insignificant become cumulatively significant. In addition, the claim that freight rates on recycled products must be increased to respond to 'emergency' revenue needs pending completion of the required, overall environmental evaluation, loses much of its force as months turn into years and the basic investigation remains uncompleted. Finally, even the 'emergency' argument itself, however legitimate, in no way forecloses the consideration of alternatives which would both meet revenue needs and at the same time avoid further potential environmental damage while the basic rate structure issue is being resolved. Alternatives of this sort were, in fact, suggested in the partial dissenting opinions of Commissioners Brown and Deason [who would have denied approval of increases for recyclable commodities], with no indication in the Commission's majority report that such measures would not have been sufficient to meet the revenue needs relied on to justify the rate increases. . . . In summary, the Council feels that the basic environmental issues related to the existing freight rate structure and

changes thereto, must be evaluated in a logical, analytical and timely fashion in compliance with the requirements of the National Environmental Policy Act. The Commission's actions to date appear to be inconsistent with the objectives of NEPA, and the analyses undertaken to date by the Commission appear to offer an inadequate basis from which to draw conclusions concerning the impact of freight rates on recycling and enviromental quality. Our staff is available to discuss the NEPA procedural issues as well as to assist in structuring the analytical work required to assess adequately the environmental impact of freight rates." [3]

The three-judge District Court held that the conclusion of the Commission that the rate increase would have "no significant adverse effect" on the environment within the meaning of EPA was "transparent" and "a ruse." 346 F. Supp., at 201. This leads to an analysis of § 102 of EPA.[4]

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[3] In his report before the Senate, Senator Jackson, as one of the three most responsible for NEPA, stated: "To insure that the policies and goals defined in this act are infuesed into the ongoing programs and actions of the Federal Government, the act also establishes some important 'action-forcing' procedures. Section 102 authorizes and directs all Federal agencies, to the fullest extent possible, to administer their existing laws, regulations, and policies in conformance with the policies set forth in this act. It also directs all agencies to assure consideration of the environmental impact of their actions in decision-making. It requires agencies which propose actions to consult with appropriate Federal and State agencies having jurisdiction or expertise in environmental matters and to include any comments made by these agencies which outline the environmental considerations involved with such proposals.

"Taken together, the provisions of section 102 directs [*sic*] any Federal agency which takes action that it must take into account environmental management and environmental quality considerations." (Congressional Record—Senate, Dec. 20, 1969, p. 40416.)

[4] The totality of § 102 is so important to this litigation that I have set it forth in Appendix II to this dissent.

That section is directed to "all agencies of the Federal Government" which of course includes the Interstate Commerce Commission. It directs the agency to interpret and administer "the policies, regulations and public laws" which it administers "to the fullest extent possible" in accordance with the policies of EPA. It directs the agency [5] to include in "major Federal actions significantly affecting the quality of the human environment" a detailed statement "by the responsible official on" "(i) the environmental impact of the proposed action, (ii) any adverse environmental effects which cannot be avoided should the proposal be implemented, (iii) alternatives to the proposed action, (iv) the relationship between local short-term uses of man's environment and the maintenance and enhancement of long-term productivity, and (v) any irreversable and irretrievable commitments of resources which would be involved in the proposed action should it be implemented. . . .

"Prior to making any detailed statement, the responsible Federal official shall consult with and obtain the comments of any Federal agency which has jurisdiction by law or special expertise with respect to any environmental impact involved. Copies of such statement and the comments and views of the appropriate Federal, State, and local agencies, which are authorized to develop and enforce environmental standards, shall be made available to the President, the Council on Environmental Quality and to the public as provided by section

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[5] Senator Jackson, one of the three most responsible for NEPA recently was reported as saying:

"We expected Section 102 of the act which requires environmental impact statements and analysis of alternatives for all major federal actions significantly affecting the quality of the human environment to force the agencies to move. . . . We did not anticipate that it would be private parties through the courts that would force the compliance. This is what has made it work." Christian Science Monitor, Feb. 28, 1973, p. —.

552 of Title 5, and shall accompany the proposal through the exciting agency review processes."

Rates affecting litter, like rates affecting other commodities, obviously are relevant to the ease and expedition with which they will be transported. To get the litter to appropriate recycling plants in the quantities needed to protect our fast depleting forests and our nonrenewable resources [6] and to relieve our landscape of the litter that plagues us may need special incentive rates.

The Conference Report 91–76J makes clear that no agency of the Federal Government is exempt and that each should comply unless existing law applicable to the agency "expressly prohibits or makes full compliance with one of the directives impossible." The Report states:

> "The purpose of the new language is to make it clear that each agency of the Federal Government shall comply with the directives set out in such subparagraphs (A) through (H) unless the existing law applicable to such agency's operations expressly prohibits or makes full compliance with one of the directives impossible. If such is found to be the case, then compliance with the particular directive is not immediately required. However, as to other activities of that agency, compliance is required. Thus, it is the intent of the conferees that the provision 'to the fullest extent possible' shall not be used by any Federal agency as a means of avoiding compliance with the directives set out in section 102. Rather, the language in section 102 is intended to assure that all agencies of the Federal Government shall

[6] Waldo E. Smith of the American Geophysical Union recently stated: "The total supply of most metals is sharply limited; even now we must dig deeper, go farther, and use lower grade ores. No optimism is justified here. The supply can be extended substantially by intelligent recycling, which should be an important by-product of our cleaning up to maintain a clean environment." Resources and Long-Forecasts, Science & Public Affairs, May 1973, 21, 22.

> comply with the directives set out in said section 'to the fullest extent possible' under their statutory authorizations and that no agency shall utilize an excessively narrow construction of its existing statutory autorizations to avoid compliance." 2 U. S. Code Cong. & Adm. News, 91st Cong., 1st Sess. 1969, p. 2770.

The District Court, acting responsibly in light of the broad and clear-cut policy of the Act concluded that it sets a "high standard" for federal agencies, that there is no "escape hatch for footdragging agencies," that the Act does not make the preparation and use of these impact statements "discretionary," that Congress did not intend for this Act to be "a paper tiger." 346 F. Supp., at 199.[7]

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[7] When Congress desires exceptions to be made to the impact statement requirement under the National Environmental Policy Act, express exemption is provided. For example, Pub. Law 92-307, 86 Stat. 191, provides that the Atomic Energy Commission can grant a temporary operating license for a nuclear power reactor without the completion of an environmental impact statement, if the application for the operating license was filed before September 9, 1971, and the Commission holds a hearing which leads to the findings, among others, that the operation of the facility during the period of the temporary operating license in accordance with its terms and conditions will provide adequate protection of the environment during the period of the temporary operating license and that the operation of the facility is essential toward insuring the power generating capacity of a utility system. The Commission is empowered to impose such terms and conditions as it deems necessary, and its decision is subject to judicial review.

Some federal agencies are taking affirmative action to promote the purposes of § 105. Thus the Securities and Exchange Commission recently adopted amendments to its registration and reporting forms to require more meaningful disclosure of certain items pertaining to the effect on the issuer's business of compliance with federal, state, and local laws and regulations relating to the protection of the environment. The amendments will require as a part of the description of the issuer's business, appropriate disclosures with respect to

Arrow Transportation Co. v. *Southern R. Co.*, 372 U. S. 658, does not preclude review here. In *Arrow* there were rates which the Commission had the power to suspend but had not done so. The power of suspension was entrusted to the Commission only; and we held that the courts should not intrude when the Commision has not acted. Here the Commission has acted; it has found that "the increases here proposed are just and reasonable, that the revenues derived therefrom will result in earnings and rates of return . . . not in excess of that required to enable" the carriers "to render adequate and efficient transportation at the lowest cost consistent with the furnishing of such service." I. C. C., at —. The Commission said it was not prescribing rates, though it attached conditions on approval of the rates without suspension. *Id.*, at —. It made clear it would suspend the new rates if the conditions were not added. As stated by the three-judge court "A suspension doctrine which effectively blackmails the carriers into submitting agency-authored rates is functionally indistinguishable from an order setting those rates." 346 F. Supp., at 197.

Moreover, as the three-judge court held and as Judge Friendly observed in *New York* v. *United States*, 337 F. Supp. 150, 164, "NEPA is a new and unusual statute imposing substantive duties which overlie those imposed on an agency by the statute or statutes for which it has jurisdictional responsibility."

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the material effects which compliance with environmental laws and regulations may have upon the capital expenditures, earnings and competitive position of the issuer and its subsidiaries. Other amendments describe the extent to which litigation disclosures should contain specific descriptions of environmental proceedings. (Letter from the Securities and Exchange Commission, Ronald Hunt, Secretary, Amend. effective July 3, 1973.) See *Scientists' Institute* v. *AEC*, — F. 2d —, decided June 12, 1973, holding that an impact statement must be filed for the Commission's liquid metal fast breeder reactor program.

The Court today greatly weakens NEPA in a crucially important segment of the federal environmental field. Movement of litter to recycling plants [8] is critically important, as Chairman Train makes abundantly clear. The alternative is to leave it underfoot or to cart if off as garbage to incinerators that pollute the air or to landfills that are getting more and more difficult to find.[9] We know that recycled paper, recycled copper, recycled iron, recycled glass is practical. The Federal Bureau of Mines in its pilot plant at Edmonston, Maryland, boasts that "urban ore," as it calls this debris, costs about $3 a ton and recycled is worth $11 a ton. We know that we deal here with nonrenewable resources. We are told that recycling paper saves thousands of acres of trees a year.[10]

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[8] Senator Jackson recently was reported as saying about these impact statements:

"We should also be able to get generic environmental impact statements—updated every six months or so—for energy policy, transportation policy, and other major policy decisions." *Supra*, n. 2, at —.

[9] Most of the Nation's waste is relocated into dumps with only approximately 10 to 15% finding its way into sanitary landfills. Science and Public Affairs, Energy Conservation and Waste Recycling, April 1973, p. 13, 17.

[10] Congressman Dingell, another main sponsor of NEPA recently was reported as saying:

"The success of the environmental impact statements is not so much that they were used as we intended they should, but that citizens have been able to use the process as a way to get into courts. . . . Some agencies are complying poorly. They decide what they are going to do and then write an environmental impact statement to support the decision. That is not what Congress had in mind. I am fearful that we are breeding a race of impact statement writers who put all the right words down but don't really get environmental concerns involved in the decision-making process. The impact statement itself is not important. The important thing is that proper judgments are made reflecting environmental considerations in the decision-making process. The impact statement should be

Under the Act, the appraisal by the Council on Environmental Quality of which Russell Train is the chairman is a weighty one for under § 201 of the Act it has the responsibility "to appraise programs and activities of the Federal Government" in light of the policy of the Act and "to formulate and recommend national policies to promote the improvement of the quality of the environment." C. E. Q. is, in other words, the expert *ombudsman* in the environmental area.

The apparent tendency among federal agencies, Congressman Dingell says,[11] is to decide first what they want to do and then prepare an impact statement as an *apologia* for what they have done. That puts the cart before the horse. That is what the Commission did here. But that is to adopt "an excessively narrow construction" of its statutory power "to avoid compliance" with the new environmental standards—all as condemned in the Conference Report, *supra*, at 2770. That is to say, environmental considerations are, so far as possible, to shape all agency policies and decisions.

These cases are, indeed, Exhibit A of the current practice of federal agencies to undermine the policy announced by Congress in NEPA. Rail rates were long discriminatory in retarding the industrial development of the South. *New York* v. *United States*, 331 U. S. 284. The present rates are arguably discriminatory against the removal of the litter which is about to engulf us. The wisdom of Chairman Train, rather than the technical maneuvers of the Commission, should be our guide.

I would affirm the judgment of the District Court.

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a discipline for this and also a process by which the public can be informed and brought into the decision-making process." *Supra*, n. 2, at —.

For a recent account of impact statements on transportation problems see Robert Cahn (former member of CEQ), Christian Science Monitor, Feb. 28, 1973, p. 12.

[11] See n. 10, *supra*.

APPENDIX I

The Bureau of Mines had at Edmonston, Maryland, for several years an incinerator residue processing plant on the basis of which Lowell, Massachusetts, instituted its Resource Recovery Project.

The Edmonston project is now engaged in recycling of raw waste and the following is the Bureau's description of the nature and scope of that project.

FACT SHEET

Edmonston (Md.) Solid Waste Recycling Project
Bureau of Mines

DEPARTMENT OF THE INTERIOR

An important part of the solid waste utilization research carried on by the Bureau of Mines is to develop methods and processes for recycling mineral materials present in urban refuse. Engineers from the Bureau's College Park (Md.) Metallurgy Research Center operate a pilot plant at Edmonston, Maryland, where they reclaim ferrous metals, nonferrous metals, glass, plastics, and paper from raw unburned refuse. The following facts are pertinent to the research underway at the Edmonston pilot plant.

xxx—100 pounds of typical municipal refuse contains:
36.6 pounds of paper and cardboard; 20.2 pounds of garbage; 8.4 pounds of metal; 8.5 pounds of glass; 17.4 pounds of leaves, grass, hedge clippings and tree prunings; 2.6 pounds of scrap wood; 1.1 pound of plastics; and 5.2 pounds of miscellaneous material including leather, rubber, textiles, bricks, stones, and dirt.

xxx—Urban refuse generated in the U. S. in 1972 totaled 300 million tons, or the equivalent of more than 8 pounds daily for every man, woman, and child.

xxx—Only 220 million tons of municipal refuse was regularly collected by public agencies and private firms. The remainder (80 million tons) was abandoned, dumped at the point of origin, or hauled to uncontrolled disposal sites.

xxx—The volume of municipal refuse accumulating in the U. S. in a single year would cover an area half the size of the State of

Connecticut (2,500 sq. mi.) with a layer of refuse 1 foot deep. This refuse contains some 12 million tons of iron and steel, 13 million tons of glass, and over a million tons of aluminum, zinc, lead, tin, and copper.

xxx—Collecting and disposing of refuse costs cities an average of $23 per ton ($18, for collection and $5, for disposal). New York City, at a cost of $40 per ton, spends almost a million dollars each day to collect and dispose of solid waste. Total U. S. bill runs about $6 billion annually.

xxx—Most municipal refuse is disposed of by dumping, landfill, or incineration. About 30 million tons of municipal refuse is burned annually in more than 300 municipal incinerators. These incinerators generate 7.5 million tons of residues, which are then buried. The process developed by the Bureau to reclaim the values from incinerator residues has attracted world-wide attention. A commercial size plant of this type will soon be under construction in Lowell, Massachusetts, with seventy-five percent of the $3.2 million required, being provided by the Environmental Protection Agency.

xxx—Successful reclamation of mineral values from incinerator residues at the Bureau's pilot plant prompted research to save also that part of municipal refuse that is now being lost during burning. This would reduce the need for building more municipal incinerators, saving their construction and operating costs, and would bring income from salvaged paper and plastics as well as metals and glass. It would also eliminate air pollution problems connected with incineration.

xxx—Equipment for mechanical separation of metals, glass, paper, and plastics from municipal refuse before incineration has been assembled at Edmonston. The process involves coarse shredding of the refuse, followed with air classification, magnetic separation, screening, optical sorting, electrostatic separation, and gravity concentration—all proven methods used in the mineral industries.

xxx—Other refuse recycling schemes have been proposed and some are already under development. The process developed by the Bureau is unique in the following major respects: (1) It is the only process that embodies a complete system, (2) it is the only process capable of capturing and concentrating putrescibles and glass, (3) it is the only process that produces a tin product suitable for detinning, (4) it is the only process capable of accepting extremely massive pieces of metal, (5) it is the only

process that can successfully separate plastics and paper, and (6) energy requirements for the Bureau's process are by far the least of all proposed processes.

xxx—A plant processing 1,000 tons of raw refuse per day could be expected to reclaim each day enough ferrous metal to make all the iron and steel parts for more than 55 4-door sedans.

xxx—About 36 billion bottles are discarded each year in the U. S. as solid waste. Each American discards a glass bottle on the average of about one every two days. The average returnable beer bottle used to make 31 round trips from the brewery, to the consumer, and back to the brewery. The average is now 19 trips. In some cities, it is only 4. People are discriminating less between returnable and non-returnable bottles.

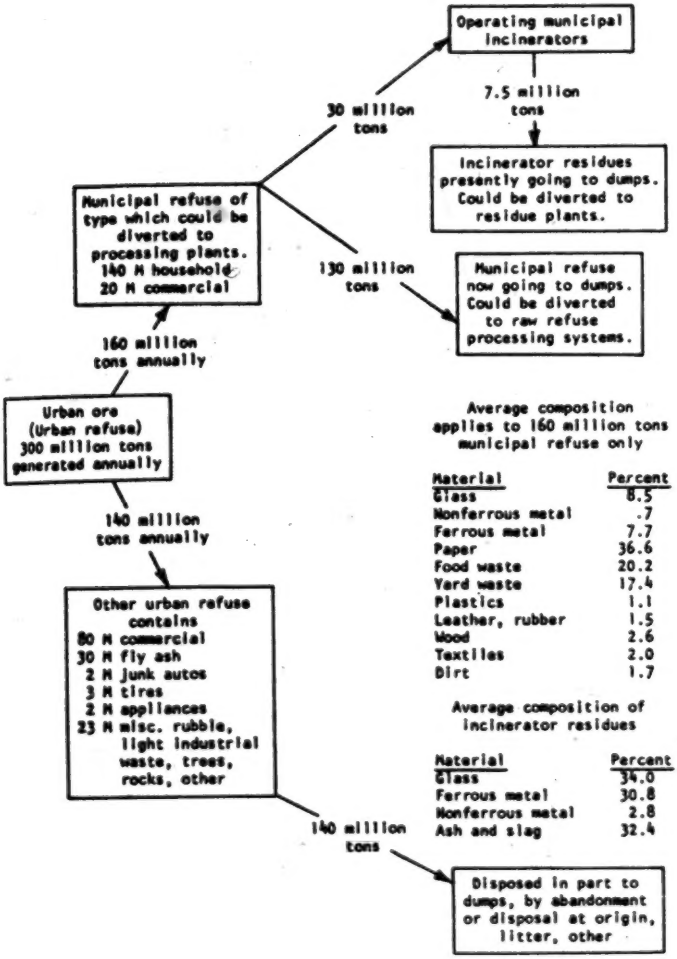
xxx—Glass reclaimed from raw refuse can be used in making new glass, or for such salable products as building bricks, mineral wool for insulation, and road surfacing (when ground and mixed with asphalt).

xxx—Aluminum present in refuse in the form of cans alone amounts to 10 percent of the total primary production. This metal together with other aluminum recovered from refuse would find a ready market at existing secondary smelters for conversion to high grade casting alloys.

xxx—The other heavy nonferrous metals could be used readily in producing brass ingot or the mixture could be further refined and separated into the constituent metals.

xxx—The rate at which we generate refuse is growing so fast that within 20 years, even if we are able to recycle 70 percent of our solid wastes our needs for landfill space will remain the same. And landfill space is, even now, becoming harder and harder to find.

URBAN REFUSE DISPOSAL IN THE UNITED STATES 1972



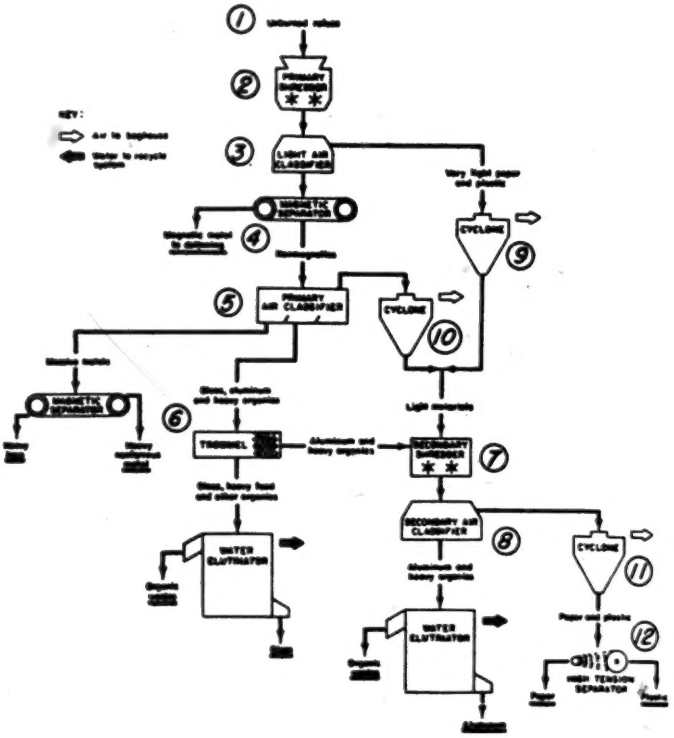
Average composition applies to 160 million tons municipal refuse only

Material	Percent
Glass	8.5
Nonferrous metal	.7
Ferrous metal	7.7
Paper	36.6
Food waste	20.2
Yard waste	17.4
Plastics	1.1
Leather, rubber	1.5
Wood	2.6
Textiles	2.0
Dirt	1.7

Average composition of incinerator residues

Material	Percent
Glass	34.0
Ferrous metal	30.8
Nonferrous metal	2.8
Ash and slag	32.4

BUREAU OF MINES DRYSORT REFUSE RECOVERY SYSTEM



APPENDIX II

Section 102 of the Environmental Protection Act, 42 U. S. C. § 4332 provides:

§ *4332. Cooperation of agencies; reports; availability of information; recommendations; international and national coordination of efforts*

The Congress authorizes and directs that, to the fullest extent possible: (1) the policies, regulations, and public laws of the United States shall be interpreted and administered in accordance with the policies set forth in this chapter, and (2) all agencies of the Federal Government shall—

(A) utilize a systematic, interdisciplinary approach which will insure the integrated use of the natural and social sciences and the environmental design arts in planning and in decisionmaking which may have a impact on man's environment;

(B) identify and develop methods and procedures, in consultation with the Council on Environmental Quality established by subchapter II of this chapter, which will insure that presently unquantified environmental amenities and values may be given appropriate consideration in decisionmaking along with economic and technical considerations;

(C) include in every recommendation or report on proposals for legislation and other major Federal actions significantly affecting the quality of the human environment, a detailed statement by the responsible official on—

(i) the environmental impact of the proposed action,

(ii) any adverse environmental effects which cannot be avoided should the proposal be implemented,

(iii) alternatives to the proposed action,

(iv) the relationship between local short-term uses of man's environment and the maintenance and enhancement of long-term productivity, and

(v) any irreversible and irretrievable commitments of resources which would be involved in the proposed action should it be implemented.

Prior to making any detailed statement, the responsible Federal official shall consult with and obtain the comments of any Federal agency which has jurisdiction by law or special expertise with respect to any environmental impact involved. Copies of such statement and the comments and views of the appropriate Federal, State, and local agencies, which are authorized to develop and enforce environmental standards, shall be made available to the President, the Council on Environmental Quality and to the public as provided by section 552 of Title 5, and shall accompany the proposal through the existing agency review processes;

(D) study, develop, and describe appropriate alternatives to recommended courses of action in any proposal which involves unresolved conflicts concerning alternative uses of available resources;

(E) recognize the worldwide and long-range character of environmental problems and, where consistent with the foreign policy of the United States, lend appropriate support to initiatives, resolutions, and programs designed to maximize international cooperation in anticipating and preventing a decline in the quality of mankind's world environment;

(F) make available to States, counties, municipalities, institutions, and individuals, advice and in-

formation useful in restoring, maintaining, and enhancing the quality of the environment;

(G) initiate and utilize ecological information in the planning and development of resource-oriented projects; and

(H) assist the Council on Environmental Quality established by subchapter II of this chapter.

Pub. L. 91–190, Title I, § 102, Jan. 1, 1970, 83 Stat. 853.

SUPREME COURT OF THE UNITED STATES

Nos. 72–535 AND 72–562

United States and Interstate Commerce Commission, Appellants, 72–535 *v.* Students Challenging Regulatory Agency Procedures (SCRAP) et al.	On Appeals from the United States District Court for the District of Columbia.
Aberdeen and Rockfish Railroad Company et al., Appellants, 72–562 *v.* Students Challenging Regulatory Agency Procedures (SCRAP) et al.	

[June 18, 1973]

MR. JUSTICE WHITE, with whom THE CHIEF JUSTICE and MR. JUSTICE REHNQUIST join, dissenting in part.

I would reverse the judgment of the District Court and order the complaint dismissed because appellees lack standing to bring this suit. None of our cases, including inferences that may be drawn from dicta in *Sierra Club* v. *Morton*, where we denied standing to petitioner there, are sufficient to confer standing on plaintiffs in circumstances like these. The allegations here do not satisfy the threshold requirement of injury in fact for constituting a justiciable case or controversy. The inquiry alleged is that the failure of the Commission to suspend a 2.5% freight rate increase may discourage the transportation of recyclable materials, thus retarding the use of recycled materials, causing further consumption of our forests and natural resources (some

of which might be taken from the Washington Metropolitan area), and resulting in more refuse and undisposable materials to further pollute the environment.

The majority acknowledges that these allegations reflect an "attentuated line of causation," *ante*, p. —, but is willing to suspend its judgment in the dim hope that proof at trial will in some unexplained way flesh them out and establish the necessary nexus between these plaintiffs and the across-the-board rate increase they complain of. To me, the alleged injuries are so remote, speculative and insubstantial in fact that they fail to confer standing. They become no more concrete, real or substantial when it is added that materials will cost more at the marketplace and that somehow the freight rate increase would increase air pollution. Allegations such as these are no more substantial and direct and no more qualify these plaintiffs to litigate than allegations of a taxpayer that governmental expenditures will increase his taxes and have an impact on his pocketbook, *Massachusetts* v. *Mellon*, 262 U. S. 447, 486–489 (1923), or allegations that governmental decisions are offensive to reason or morals. The general "right, possessed by every citizen, to require that the Government be administered according to law and that public monies not be wasted" does not confer standing to litigate in federal courts. *Fairchild* v. *Hughes*, 258 U. S. 126, 129 (1922). New York did not have standing to complain when it asserted merely the possible adverse effects of diversion of water from Lake Michigan upon hypothetical power developments in "the indefinite future." *New York* v. *Illinois*, 274 U. S. 488, 490 (1927). Assumed potential invasions are insufficient basis for a justiciable case and controversy. *Arizona* v. *California*, 283 U. S. 423, 462 (1931). As I see the allegations in this case, they are in reality little different from the general interest allegations found insufficient and too remote in

Sierra Club. If they are sufficient here, we are well on our way to permitting citizens at large to litigate any decisions of the Government which fall in an area of interest to them and with which they disagree.

Assuming, however, that a majority of the Court adheres to the conclusion that a constitutional case or controversy exists in these circumstances and that plaintiffs may sue, I would agree that the District Court erred in entering an injunction which Congress quite clearly had long since divested it of the power to enter. Accordingly, I join Part III of the Court's opinion. I add only that failure to maintain this country's railroads even in their present anemic condition will guarantee that recyclable materials will stay where they are—far beyond the reach of recycling plants that as a consequence may not be built at all.

SUPREME COURT OF THE UNITED STATES

Nos. 72–535 AND 72–562

United States and Interstate Commerce Commission, Appellants, 72–535 *v.* Students Challenging Regulatory Agency Procedures (SCRAP) et al. Aberdeen and Rockfish Railroad Company et al., Appellants, 72–562 *v.* Students Challenging Regulatory Agency Procedures (SCRAP) et al.	On Appeals from the United States District Court for the District of Columbia.

[June 18, 1973]

MR. JUSTICE MARSHALL, concurring in part and dissenting in part.

I fully agree with and join in Part II of the Court's opinion wherein it sustains the District Court's determination that the appellees have standing to challenge the 2.5% interim surcharge on the ground that the Interstate Commerce Commission's order of April 24 permitting the surcharge to take effect was not issued in compliance with the requirements of the National Environmental Policy Act of 1969 (NEPA), 42 U. S. C. §§ 4321–4347. The Court goes on, however, to hold in Part III of its opinion that the District Court lacked power to issue a preliminary injunction barring implementation of the surcharge due to the Commission's alleged failure to comply with NEPA in the suspension

stage of the rate proceeding. The Court's decision in this respect is, to be sure, a very narrow one; the decision clearly concerns only the scope of remedies available to the District Court in the context of a case of this particular character,[1] that is, an ICC rate suspension case. The Court specifically refrains from deciding whether or not the Commission's alleged failure to comply with NEPA in the suspension stage is a proper subject for judicial review, and if so, what would constitute adequate compliance with NEPA at that juncture in the administrative process. See *ante*, at 27 n. 22. Nonetheless, I am unable to join the third portion of the Court's opinion, for I am convinced that there is no lack of judicial power to issue a preliminary injunction against the interim surcharge in the context of this case. I therefore must respectfully dissent from Part III of the Court's opinion.

At the outset, it is essential for purposes of analysis to put the issue upon which the Court disposes of the case in proper perspective. Since the Court addresses only the issue of the District Court's power to grant preliminary relief, we must, of course, assume for the sake of argument that the issues which the Court does not now reach—namely, whether the procedural requirements of NEPA[2] are applicable at the suspension stage and

[1] Given that the Court holds only that the District Court lacked power to grant preliminary injunctive relief, it presumably remains open to appellees to challenge the Commission's alleged failure to comply with NEPA in the suspension stage of the proceedings concerning the interim surcharge in an action for declaratory relief. Nor does anything in the Court's opinion today deny to the District Courts power to enjoin the Commission to comply with NEPA in the context of a particular rate proceeding so long as no injunction is issued barring implementation of the rates themselves, cf. *Atchison, T. & S. F. R. Co.* v. *Wichita Board of Trade*, *ante*, p. —.

[2] See in particular § 102 (2)(C) of the Act, 42 U. S. C. § 4332 (2)(C).

whether the issue of Commission compliance is a proper one for judicial review [3]—are to be decided in appellees' favor. In addition, we must accept for the present appellees' assertions that the interim surcharge, by raising the cost of shipping recyclable materials, will further accentuate the allegedly unjustifiable disparity between the cost of shipping those materials and the cost of shipping primary goods, thereby irrationally encouraging the use of primary goods which will lead to a further degradation of our environment. In other words, in considering the question of judicial power, we must accept the correctness of the District Court's determination that there was a "strong likelihood" that the Commission had erred in its conclusion that the interim surcharge " 'will have no significant adverse effect on . . . the quality of the human environment within the meaning of the Environmental Policy Act of 1969,' " 346 F. Supp., at 200, 201, a conclusion that had effectively excused the Commission from compliance with the procedural requirements of NEPA in the context of the surcharge, see 42 U. S. C. § 4332 (2)(C).

Turning then to the issue of judicial power, it must first be recalled that we deal here with the grant of only a preliminary injunction; the District Court did not permanently enjoin enforcement of the interim surcharge upon determining that the Commission had, in all likelihood, failed to comply with NEPA in the suspension stage. Properly viewed, I think the injunction at issue in this case amounts to nothing more than a legitimate effort by the District Court, following the Commission's refusal to suspend the surcharge, to maintain the *status*

[3] Cf., *e. g.*, *Upper Pecos Assn.* v. *Stans*, 452 F. 2d 1233 (CA10 1971), vacated and remanded for consideration of mootness *sub nom. Upper Pecos Assn.* v. *Peterson*, 409 U. S. 1021 (1972); *Calvert Cliffs' Coordinating Comm'n* v. *United States AEC*, — U. S. App. D. C. —, 449 F. 2d 1109 (1971); *City of New York* v. *United States*, 337 F. Supp. 150, 158–160 (EDNY 1971).

quo pending final judicial determination of the legality of the Commission's action at the suspension stage in light of the requirements of NEPA. And, by now, the equitable power of the federal courts to grant interim injunctive relief pending determination of an appeal is well established. The nature of that power was explored at length by the Court in *Scripps-Howard Radio, Inc.* v. *FCC*, 316 U. S. 4 (1942), where it was held that a court of appeals had power, pending determination of an appeal, to stay the Federal Communications Commission's grant of a construction permit although the Federal Communications Act made no provision for such a stay. Speaking for the Court, Mr. Justice Frankfurter explained:

> "No court can make time stand still. The circumstances surrounding a controversy may change irrevocably during the pendency of an appeal, despite anything a court can do. But within these limits it is reasonable that an appellate court should be able to prevent irreparable injury to the parties or to the public resulting from premature enforcement of a determination which may later be found to have been wrong. It has always been held, therefore, that as a part of its traditional equipment for the administration of justice, a federal court can stay the enforcement of a judgment pending the outcome of an appeal." *Id.*, at 9–10. See also *FTC* v. *Dean Foods Co.*, 384 U. S. 597, 604 (1966); *Whitney National Bank in Jefferson Parish* v. *Bank of New Orleans & Trust Co.*, 379 U. S. 411, 425 (1965).

This Court has consistently adhered to the view that it will find federal courts to have been deprived of their traditional power to stay orders under review only in the face of the clearest possible evidence of a congressional intent to do so. See *Scripps-Howard Radio, Inc.* v. *FCC*, 316 U. S., at 11, 15. No such clear intent is to

be found in the Interstate Commerce Act, at least not with respect to a case such as this where the Commission has already acted on the relevant issue and the issue lies in an area outside the Commission's traditional expertise.[4] In *Arrow Transportation Co.* v. *Southern Railway Co.*, 372 U. S. 658, 664 (1963), this Court specifically acknowledged that "[i]t cannot be said that the legislative history of the grant of suspension power to the Commission includes unambiguous evidence of a design to extinguish whatever judicial power may have existed prior to [the establishment of suspension powers in the Commission] to suspend proposed rates." The *Arrow* Court was asked to extend by injunction the statutory seven-month suspension period, see 49 U. S. C. § 15 (7), because the Commission had not reached a decision on the lawfulness of the proposed rates at the end of the suspension period and the rail carriers, following a period of voluntary suspension, were threatening to implement the rate change without awaiting final agency action. Despite the ambiguity of the legislative history, the Court, upon careful examination of the character of and reasons for the suspension scheme, concluded that Congress must have intended to deprive the federal courts of the power to suspend rates pending completion of agency action and thus that the traditional equitable powers of the federal courts had been overriden to that extent. But as detailed consideration of the factors that motivated the decision in *Arrow* reveals, this case presents a significantly different problem.

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[4] Thus, I cannot accept the Court's assertion that the question in this case is "whether in a specific context NEPA *sub silentio* revived judicial power that had been explicitly eliminated by Congress." *Ante*, at 24. That is a question which I do not believe need ever be reached here, for—as shall be seen—Congress has not, to begin with, deprived the federal courts of their traditional equitable powers in the context of this case.

The *Arrow* Court felt that an injunction extending the suspension period pending final agency action would involve a serious, unintended intrusion on the primary jurisdiction of the Commission. This problem of primary jurisdiction had two aspects in *Arrow*. First, where the issue is the reasonableness of proposed rates, an application for an injunction against implementation of those rates pending final agency action would necessarily require a federal court "to pass before final Commission action upon the question of reasonableness of a rate," 372 U. S., at 671, thereby providing, in effect, an advisory judicial opinion to the Commission on an issue which Congress intended that the Commission decide in the first instance. Certainly, the Commission's expertise in matters of rail carrier operations and economics is well recognized, and *Arrow* clearly indicates that the courts should not interfere with the exercise of that expertise. However, the grant of preliminary relief in this case involves no such interference with the Commission's inital exercise of its particular expertise.

So far as I am aware, the Commission has never been deemed especially expert in matters of environmental policy or impact.[5] It is, of course, true that the Commission must decide in the first instance whether particular proposed action constitutes "major Federal action significantly affecting the quality of the human environment," thus necessitating agency compliance with the detailed requirements of § 102 (2)(C) of NEPA, 42 U. S. C. § 4332 (2)(C). But that decision had already been made in this case *prior to* the time when judicial intervention by the District Court was sought—in contrast to the situation in *Arrow* where the question of the reasonableness of the rates remained unresolved by the

[5] Administrative expertise in such matters is surely lodged with the Environmental Protection Agency and the Council on Environmental Quality.

Commission. Even assuming that some element of agency expertise is involved in the decision at issue here, the District Court, in granting preliminary relief against the interim surcharge, passed only upon a question of which the Commission had finally disposed, namely, the environmental impact of not suspending the interim surcharge and of permitting it to take effect at once. Thus, for purposes of the particular issue raised in this case, the District Court was presented with final agency action[6] and was not in danger of interfering with the Commission's expertise when it stayed the Commission's order pending final determination of the appeal.[7]

The other aspect of the problem of primary jurisdiction focused upon in *Arrow* was the timing of the implementation of new rates. The Court concluded that Congress had intended that the Commission should determine when new rates should take effect. See 372 U. S., at 668. Insofar as the economic impact of rate increases was concerned, Congress enacted a scheme which permitted the Commission to take into account the interests of both rail carriers and shippers. Thus, Congress recognized that economic necessity might persuade the Commission to permit otherwise questionable rates to go unsuspended while they were being investigated, and, at most, it allowed the Commission to suspend proposed rates for only seven months, see 49 U. S. C. § 15 (7). At the same time, Congress attempted to accommodate the economic interests of shippers, for it gave the Commission power, pending final agency action, to require the rail carriers to maintain detailed records of monies received due to the increase and to compel payment of

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[6] Cf. L. Jaffe, Judicial Control of Administrative Action 688 (1965).

[7] Contrast *Atchison, T. & S. F. R. Co.* v. *Wichita Board of Trade*, *ante*, p. —.

refunds if a rate increase was ultimately found to be unreasonable.[8] See *ibid.*

But where does the Interstate Commerce Act make provision for an accounting and "refund" to the people of our Nation for the irreversible ecological damage that results from a rate increase which discriminates unreasonably against recyclable materials and has been allowed to take effect without compliance with the procedural requirements of NEPA?[9] The Court today says that

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[8] Moreover, even if the Commission fails to require record keeping and the payment of refunds *sua sponte*, Congress also provided a mechanism by which shippers may initiate an action before the Commission to seek reparations from a carrier on the ground that particular rates are unreasonable. See 49 U. S. C. § 13 (1).

Arrow, to be sure, did not involve an economic dispute between shippers and rail carriers, but was, instead, an action brought by water carriers who contended that certain challenged decreases in the rates of competing rail carriers were designed to destroy them rather than the result of legitimate economic considerations. Obviously, the refund and reparation provisions of the Interstate Commerce Act were of no more value to the water carriers in *Arrow* than they are to the nonshipper appellees in this case. But, as the Court pointed out in *Arrow*, "[c]onflicts over rates between competing carriers were familiar to the Commission long before [the enactment of the suspension provisions] . . . . Indeed, in another provision of the very same statute [that established the suspension powers] Congress . . . dealt explicitly with *reduction* of rates by railroads competing with water carriers [—namely, 49 U. S. C. §4 (2)]. In addition § 8 of the Act, 49 U. S. C. § 8, creates a private right of action for damages—based on conduct violative of the Act—which might be available . . . ." 372 U. S., at 669. Thus, Congress had taken into account, and had provided for, disputes between competing carriers, as well as between shippers and carriers, in enacting the suspension provisions. The same can hardly be said for conflicts between the environmental policies of NEPA and the Commission's suspension power.

[9] Indeed, given the substantial element of public interest at stake in a case such as this, it is appropriate to recall Justice Stone's oft-quoted admonition: "Courts of equity may, and frequently do, go much further both to give and withhold relief in furtherance of the

"[t]o allow judicial suspension for noncompliance with NEPA, would disturb the careful balance of interests" struck by Congress in the suspension and refund provisions. *Ante*, at 25–26. Yet the simple fact is that in the carefully designed suspension and refund scheme no balance was struck with respect to the environmental interests that have been recognized by Congress in NEPA *since* the introduction of the suspension provisions into the Interstate Commerce Act. Under these circumstances, we can hardly infer an intent on the part of Congress to deprive the federal courts of their traditional responsibility, in passing upon a request for equitable relief, to work an accommodation in each particular case of the competing interests of the relevant parties [10]—that is, of a rail carrier's alleged need for increased income that will otherwise be forever lost each day that the new rate is not changed and of the extent of irreversible environmental damage that might result if the rates are not suspended. The District Court, in its effort to preserve the *status quo* pending final review of the Commission's April 24 order, gave full consideration to the effects on all parties of either granting or denying preliminary relief against the interim surcharge.[11] In then temporarily enjoining the surcharge, I believe that the District Court acted within the scope of its legitimate powers.

To summarize, then, I obviously cannot agree with the Court's assertion that "each of the policies that we

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public interest than they are accustomed to go when only private interests are involved." *Virginia R. Co.* v. *Systems Federation No. 40*, 300 U. S. 515, 552 (1937).

[10] Cf. *Hecht Co.* v. *Bowles*, 321 U. S. 321, 329–330 (1944).

[11] Thus, the District Court, fully recognising the financial plight of the rail carriers, carefully limited its preliminary injunction to the application of the interim surcharge to recyclable materials, "allowing [the rail carriers] to collect the surcharge on all nonrecyclable goods." 346 F. Supp., at 202.

identified in *Arrow* as the basis for § 15 (7) would be substantially undermined if the courts were found to have suspension powers simply because noncompliance with NEPA was alleged." *Ante*, at 25. In *Arrow* itself, the Court was at pains to point out that its decision did not "reflect in any way upon decisions which have recognized a limited judicial power to preserve the court's jurisdiction or maintain the *status quo* by injunction pending review of an agency's action through prescribed statutory channels." 372 U. S., at 671 n. 22. True, the Court went on to say there that "[s]uch power . . . has never been recognized in derogation of such a clear congressional purpose to oust judicial power as that manifested in the Interstate Commerce Act." *Ibid.* But the import of that remark must be judged with a full understanding of the factors underlying the *Arrow* Court's find of "such a clear congressional purpose." As has been seen, close analysis of those factors identified certainly does not compel extension of the *Arrow* holding to the request for preliminary injunctive relief in this case.[12] The Court would do well to re-

[12] The *Arrow* Court also pointed out that experience with judicial injunctions against rates prior to the establishment of the Commission's suspension powers in § 15 (7) had "resulted in disparity of treatment as between different shippers, carriers, and sections of the country, causing in turn 'discrimination and hardship to the general public.'" 372 U. S., at 664. These results were due both to the conflicting views of lower federal courts as to their power to enjoin rates pending agency determination of their lawfulness and conflicting judgments of different courts as to the reasonableness of the same rates. See. *id.*, at 663–664. But the danger of conflicting judgments concerning the same rates and unevenhanded treatment of shippers and carriers, merely because of the fortuity of the particular judicial district in which they are located, is not present where, as here, the allegation is that the Commission has failed to follow the requirements of a statute—NEPA—relevant to the exercise of its regulatory jurisdiction and the Commission has, as a consequence, been joined in the suit as a defendant. So long as the Commission has been

member that "[w]here Congress wished to deprive the courts of [their] historic powers [to enjoin orders pending review], it knew how to use apt words . . . ." *Scripps-Howard Radio, Inc.* v. *FCC*, 316 U. S., at 17. Cf. *Hecht Co.* v. *Bowles*, 321 U. S. 321, 329 (1944). Nothing in the language of the Interstate Commerce Act or in the particular structure of that Act or even in our decision in *Arrow* compels the conclusion that Congress has done so here. I must therefore dissent from the Court's ultimate disposition of this case.

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made a party, it is possible to ensure uniformity of treatment by enjoining the Commission to exercise its suspension powers where a failure to comply with NEPA is believed to exist. This is what the District Court did here when it enjoined the Commission "from permitting . . . the 2.5 percent surcharge" to be collected by the rail carriers "pending further order of this court." See Jurisdictional Statement, at 30a. It may be that the danger of conflicting results where the Commission has not been made a party would warrant a court staying its hand, but that is not a problem in this case.

NOTE: Where it is feasible, a syllabus (headnote) will be released, as is being done in connection with this case, at the time the opinion is issued. The syllabus constitutes no part of the opinion of the Court but has been prepared by the Reporter of Decisions for the convenience of the reader. See *United States* v. *Detroit Lumber Co.*, 200 U.S. 321, 337.

SUPREME COURT OF THE UNITED STATES

Syllabus

WEINBERGER ET AL. *v.* BENTEX PHARMACEUTICALS, INC., ET AL.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 72–555. Argued April 17, 1973—Decided June 18, 1973

Respondent drug marketers filed suit for a declaratory judgment that their drugs containing pentylenetetrazol are generally recognized as safe and effective and thus are not "new drugs" within the meaning of § 201 (p) of the Federal Food, Drug, and Cosmetic Act of 1938, as amended. They also sought exemption under § 107 (c) (4), the grandfather clause, of the 1962 amendments to the Act. The Food and Drug Administration (FDA) Commissioner, based on NAS–NRC panel reports, concluded that there was a lack of substantial evidence that the drugs were effective for their intended uses and gave notice of his intention to initiate proceedings to withdraw approval of the new drug applications (NDA's). In light of the FDA's position that withdrawal of approval of an NDA would operate to remove marketing approval for all drugs of similar composition, known as "me-too" drugs, whether or not expressly covered by an effective NDA, the Commissioner invited holders of NDA's for drugs containing pentylenetetrazol "and any interested person who might be adversely affected by their removal from the market" to submit "adequate and well-controlled studies" to establish the effectiveness of the drugs. Only one NDA holder submitted further evidence, which the Commissioner held did not satisfy the statutory standard. He gave notice of intent to issue an order withdrawing approval of the NDA's, and only one NDA holder requested a hearing but filed no supporting data. The Commissioner issued orders withdrawing approval of the NDA's and no appeal was taken. Respondents here all market "me-too" drugs, none of which was expressly covered by an effective NDA. The District Court held that the FDA should resolve the "new drug" and "grandfather" issues in an administrative proceeding. The Court of Appeals

Syllabus

reversed and remanded with directions to the District Court to determine whether the challenged drugs may lawfully be marketed without approved NDA's, holding that the FDA has no jurisdiction, primary or concurrent, to decide what is a "new drug" for which an NDA is required.

Held: The District Court's referral of the "new drug" and "grandfather" issues to the FDA was proper. Pp. 3–9.

(a) While an FDA order denying an NDA and withdrawing one is reviewable by the Court of Appeals under § 505 (h), an order declaring a "new drug" status under § 201 (p) is reviewable under the Administrative Procedure Act by the District Court. Pp. 5–6.

(b) The reach of scientific inquiry under both § 505 (d) and § 201 (p) is the same, *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, *ante*, p. —, and it is implicit in the regulatory scheme that the FDA has jurisdiction to decide with administrative finality, subject to judicial review, the "new drug" status of individual drugs or classes of drugs. Pp. 6–7.

(c) The "new drug" and "grandfather" issues are peculiarly suited to initial determination by the FDA with its specialized competence and expertise. Pp. 8–9.

463 F. 2d 363, reversed.

DOUGLAS, J., delivered the opinion of the Court, in which all Members joined, except BRENNAN, J., who took no part in the consideration or decision of the case, and STEWART, J., who took no part in the decision of the case.

NOTICE: This opinion is subject to formal revision before publication in the preliminary print of the United States Reports. Readers are requested to notify the Reporter of Decisions, Supreme Court of the United States, Washington, D.C. 20543, of any typographical or other formal errors, in order that corrections may be made before the preliminary print goes to press.

SUPREME COURT OF THE UNITED STATES

No. 72–555

Caspar W. Weinberger, Secretary of Health, Education, and Welfare, et al., Petitioners, v. Bentex Pharmaceuticals, Inc., et al.

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit.

[June 18, 1973]

MR. JUSTICE DOUGLAS delivered the opinion of the Court.

In this case Bentex and some 20 other firms that market drugs containing pentylenetetrazol filed this suit for a declaratory judgment that their drugs containing pentylenetetrazol are generally recognized as safe and effective and thus not "new drugs" within the meaning of § 201 (p)(1) of the Federal Food, Drug, and Cosmetic Act of 1938 as amended, 21 U. S. C. § 321 (p)(1). They also sought exemption from the new effectiveness requirements by reason of § 107 (c)(4) of the 1962 amendments to the Act, known as the "grandfather" clause.

As part of FDA's Drug Efficacy Study Implementation program, three separate NAS–NRC panels reviewed the evidence concerning these drugs, and each concluded that the drug was "ineffective" for the indicated use. The Commissioner concluded there was a lack of substantial evidence that these drugs were effective for their intended uses and gave notice announcing his intention to initiate proceedings to withdraw approval of the NDAs. FDA had taken the position that withdrawal of approval of an

NDA would operate to remove marketing approval for all drugs of similar composition, known as "me-too" drugs, whether or not they were expressly covered by an effective NDA.[1] Accordingly, the notice invited the holders of the NDAs for drugs containing pentylenetetrazol "and any interested person who might be adversely affected by their removal from the market" to submit "adequate and well-controlled studies" to establish the effectiveness of the drugs. See § 505 (d), 21 U. S. C. § 355 (d). Only one NDA holder submitted further evidence, which the Comissioner held did not satisfy the statutory standard. He thereupon gave notice of intent to issue an order withdrawing approval of the NDAs under § 505 (3), 21 U. S. C. § 355 (e). Again, all those who might be adversely affected by withdrawal of the NDAs were given the opportunity to participate. Only one NDA holder requested a hearing but filed no data to support it. The Commission issued orders withdrawing approval of the three NDAs (35 Fed. Reg. 14412); no appeal was taken. This suit in the District Court followed. It appears that all of the parties to this suit market "me-too" drugs, none of which was expressly covered by an effective NDA.

The District Court held that although it could determine whether the drugs were "new" or "grandfathered" drugs, its jurisdiction was concurrent with that of FDA

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[1] 37 Fed. Reg. 23185–23187, adding § 130.40 to 21 CFR, defines "identical, related, or similar drug" as used in this Act to include "other brands, potencies, dosage forms, salts, and esters of the same drug moiety as well as of any drug moiety related in chemical structure or known pharmacological properties." It also provides all persons with an interest in such drugs an opportunity for hearing on any proposed withdrawal of NDA approval for the basic drug. A district court order, — F. Supp. —, directing FDA to apply the NAS–NRC evaluation to all "me-too" drugs is reproduced in 37 Fed. Reg. 26623–26624.

and that FDA should resolve the "new drug" issue in an administrative proceeding. — F. Supp. —. It entered an injunction to preserve the status quo and ruled that if FDA should decline to hold a hearing it would determine the issue. The Court of Appeals reversed and remanded with directions that the District Court determine whether the challenged drugs may lawfully be marketed without approved NDAs. — F. 2d —. It held that FDA has no jurisdiction, either primary or concurrent, to decide in an administrative proceeding what is a "new drug" for which an NDA is required. In its view the 1962 Act established two forums for the regulation of drugs: an administrative one for premarketing clearances for "new drugs" or withdrawal of previously approved NDAs with the right of appeal; and second, a judicial one for enforcement of the requirement that "new drugs" be cleared as safe and effective before marketing by providing the Government with judicial remedies of seizure, injunction and criminal prosecution available solely in the District Court. *Id.*, at —.

We reverse the Court of Appeals.

FDA, as a result of an NAS–NRC study and after due notice, faced up to the problem of proposing withdrawal on drugs found to be lacking in substantial evidence of effectiveness. One method would be to have 1,000 withdrawal hearings—perhaps as many as 3,500, each one lasting probably for weeks. The cost in time and budget would be enormous. Accordingly, FDA issued regulations,[2] already discussed in the *Hynson* cases, *ante*, defining the "scientific principles which characterize an adequate and well-controlled clinical investigation," [3] which elaborates on the statutory "substantial evidence" test. And as we held in the *Hynson* cases, no basis for

[2] 35 Fed. Reg. 3073, 35 Feg. Reg. 7250.

[3] See the Appendix in the *Hynson* cases.

a hearing under these regulations would be laid unless a party seeking a hearing proffered at least some evidence of that nature and quality.

By May 1972, 102 final orders effecting withdrawal of approval for 452 NDAs had been issued; and they resulted in the removal from the market of an additional 1,473 "me-too" drugs.[4] FDA was still troubled because under the 1962 Act no census of the marketplace was authorized. That is why Congress enacted the Drug Listing Act of 1972, 86 Stat. 559, — U. S. C. —. That Act requires manufacturers to submit to FDA a list of all drugs they market, including data showing their composition, labeling, and advertising.[5] The Senate Report stated: [6]

> "The effective enforcement of the drug provisions of the Act requires the ready availability of a current inventory of all marketed drugs. The Secretary is just completing a thorough review of the effectiveness of drugs marketed pursuant to new drug applications during the period 1938–1962, as required by the Drug Amendments of 1962. Application of the results of this important review to related drugs would be frustrated if a list of all marketed drugs were not easily obtained."

FDA also realized that it is impossible to apply the 1962 amendments to over-the-counter (OTC) drugs on a case-by-case basis. There are between 100,000 and 500,000 of these products, few of which were previously

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[4] Hearings on the Present Status of Competition in the Pharmaceutical Industry before the Subcommittee on Monopoly of the Senate Select Committee on Small Business, 92d Cong., 2d Sess., pt. 22, at 8525.

[5] Filings are due in June 1973. 37 Fed. Reg. 26432.

[6] S. Rep. No. 92–924, 92d Cong., 2d Sess., p. 2.

approved by FDA. In May 1972 FDA adopted a procedure for determining whether particular OTC products, not covered by NDAs are safe products, not ineffective, and not misbranded. 37 Fed. Reg. 9464. The procedure involves the establishment of independent expert panels for different categories of OTC drugs (*e. g.*, antacids, laxatives, analgesics) which would review all available data and prepare monographs prescribing drug composition, labeling, and manufacturing controls. OTCs conforming to the monograph will not be considered either misbranded or a "new drug" requiring an NDA. The regulation provides for a hearing before the expert panel, comments and rebuttal comments on the monograph and finally a hearing before the Commissioner and judicial review. *Id.*, at 9475.

This case, like the cross-petition in the *Hynson* case (72–414) raises the question whether FDA has authority to decide in an administrative hearing whether a drug satisfies the new effectiveness requirements of the Act. As noted, the Commissioner ordered that three NDAs for the drugs in question be withdrawn. Review order was not sought in the Court of Appeals as provided in § 505 (h), 21 U. S. C. § 355 (h). Rather, the aggrieved manufacturers of "me-too" drugs filed suit in the District Court, with the results we have already detailed. The narrow question is whether the FDA may decide whether a drug is a "new drug" on referral from a district court.

As already noted, an order denying an NDA and withdrawing one is reviewable by the Court of Appeals, § 505 (h); and we see no reason why Congress could not make one method of review the exclusive one. Certainly an order that does not deny or withdraw an NDA is reviewable under the Administrative Procedure Act, if it declares a "new drug" status. See *Hynson* cases, *ante*,

at —. In bolstering that conclusion we should note in passing that *Abbott Laboratories* v. *Gardner*, 387 U. S. 136, 144, said that the provisions stated in this Act for judicial review do not manifest "a congressional purpose to eliminate judicial review of other kinds of agency action." While § 505 (h) would appear to be the exclusive method of obtaining judicial review of FDA's order withdrawing an NDA covering the instant drugs, the Government apparently did not oppose the District Court's taking jurisdiction nor appeal from its action and presents no objection to the exercise by the courts of jurisdiction in this case. It does, however, strenuously oppose the conclusions reached by the Court of Appeals.

That court, in holding that FDA has no jurisdiction to determine the "new drug" status of a drug, stated that the question of "new drug" status is never presented when an application of a manufacturer for approval is filed. Parties, of course, cannot confer jurisdiction; only Congress can do so. The line sought to be drawn by the Court of Appeals is FDA action on NDAs pursuant to § 505 (d) and § 505 (e) on the one hand and the question of "new drug" determination on the other. We can discern no such jurisdictional line under the Act. The FDA, as already stated, may deny an NDA where there is a lack of "substantial evidence" of the drug's effectiveness, based as we have outlined on clinical investigation by experts. But the "new drug" definition under § 201 (p) encompasses a drug "not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use." Whether a particular drug is a "new drug," depends in part on the expert knowledge and experience of scientists based on controlled clinical experimentation and backed by substantial support in scientific literature. One function is not peculiar to

judicial expertise, the other to administrative expertise. The two types of cases overlap and strongly suggest that Congress desired that the administrative agency make both kinds of determinations. Even where no such administrative determination has been made and the issue arises in a district court in enforcement proceedings, it would be commonplace for the court to await an appropriate administrative declaration before it acted. See *Myers* v. *Bethlehem Shipbuilding Corp.*, 303 U. S. 41, 50–51; *Federal Power Commission* v. *Louisiana Power & Light Co.*, 406 U. S. 621, 647. It may, of course, be true that in some cases general recognition that a drug is efficacious might be made without the kind of scientific support necessary to obtain approval of an NDA. But as we indicate in the *Hynson* cases, *ante*, at —, the reach of scientific inquiry under both § 505 (d) and under § 201 (p) is precisely the same.

We think that it is implicit in the regulatory scheme, not spelled out in *heac verba*, that FDA has jurisdiction to decide with administrative finality, subject to the types of judicial review provided, the "new drug" status of individual drugs or classes of drugs. The deluge of litigation that would follow if "me-too" drugs and OTC drugs had to receive *de novo* hearings in the courts would enure to the interests of manufacturers and merchants in drugs, but not to the interests of the public that Congress was anxious to protect by the 1962 amendments, as well as OTC drugs and drugs covered by the 1972 Act. We are told that FDA is incapable of handling a caseload of more than perhaps 10 or 15 *de novo* judicial proceedings in a year. Clearly, if FDA were required to litigate, on a case-by-case basis, the "new drug" status of each drug now marketed, the regulatory scheme of the Act would be severely undermined, if not totally destroyed. Moreover, a case-by-case approach is inherently unfair because it requires compliance by one

manufacturer while his competitors marketing similar drugs remain free to violate the Act. In a case much more clouded with doubts than this one, we held that we would not "in the absence of compelling evidence that such was Congress' intention . . . prohibit administrative action imperative for the achievement of an agency's ultimate purposes." *Permian Basin Area Rate Cases*, 390 U. S. 747, 780. And see *Ricci* v. *Chicago Mercantile Exchange*, 409 U. S. 289, 304–306.

We conclude that the District Court's referral of the "new drug" and the "grandfather" issues to FDA was appropriate, as these are the kinds of issues peculiarly suited to initial determination by the FDA. As the District Court said: "Evaluation of conflicting reports as to the reputation of drugs among experts in the field is not a matter well left to a court without chemical or medical background." — F. Supp., at —. The determination whether a drug is generally recognized as safe and effective within the meaning of § 201 (p)(1) necessarily implicates complex chemical and pharmacological considerations. Threshold questions within the peculiar expertise of an administrative agency are appropriately routed to the agency, while the court holds its hand. As we stated in *Far Eastern Conference* v. *United States*, 342 U. S. 570, 574–575: ". . . in cases raising issues of fact not within the conventional experience of judges or cases requiring the exercise of administrative discretion, agencies created by Congress for regulating the subject matters should not be passed over. This is so even though the facts after they have been appraised by specialized competence serve as a premise for legal consequences to be judicially defined. Uniformity and consistency in the regulation of business entrusted to a particular agency are secured, and the limited functions of review by the judiciary are more rationally exercised, by preliminary resort for ascertaining and interpreting the circumstances

underlying legal issues to agencies that are better equipped than courts by specialization, by insight gained through experience, and by more flexible procedure." And see *Port of Boston Marine Terminal Association* v. *Rederiaktubolaget Transatlantic*, 400 U. S. 62, 68; *Ricci* v. *Chicago Mercantile Exchange*, *supra*, at 304–306.

Reversed.

MR. JUSTICE BRENNAN took no part in the consideration or decision of this case. MR. JUSTICE STEWART took no part in the decision of this case.

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SUPREME COURT OF THE UNITED STATES

Syllabus

USV PHARMACEUTICAL CORP. *v.* WEINBERGER ET AL.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FOURTH CIRCUIT

No. 72-666. Argued April 17, 1973—Decided June 18, 1973

Petitioner sells drug products containing citrus bioflavonoid, an extract from fruit skins, as a principal active ingredient. In the 1950's new drug applications (NDA's) were filed and became effective for seven products, and two were sold without any NDA. After the enactment of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act, these products, together with a large number of other bioflavonoid products were examined by the Food and Drug Administration for effectiveness. Based upon NAS–NRC reports and its own evaluation, FDA gave notice of opportunity for hearing on its proposal to withdraw approvals of NDA's for all drugs containing these compounds, alone or in combination with other drugs. Petitioner then brought suit in the District Court, seeking a declaratory judgment that its drugs are exempt from the efficacy requirements under § 107 (c)(4), the so-called "grandfather" clause. The FDA refused a stay pending the judicial proceedings and went forward with its administrative action. Petitioner submitted no evidence of "adequate and well-controlled investigations" as required by § 505 (d) to support its claims of effectiveness, and the FDA withdrew petitioner's NDA's. Section 107 (c)(4) exempts from the effectiveness requirements any drug which on the day preceding the 1962 enactment (1) was commercially used or sold in the United States, (2) was not a "new drug" as defined in the 1938 Act, and (3) "was not covered by an effective application" for a new drug under the 1938 Act. The District Court found that two of the products had never been covered by effective NDA's and that, while seven had been covered, their applications had later been withdrawn by petitioner. It concluded that petitioner's drugs were not covered by effective applications, and hence were exempt from the

effectiveness criterion. The Court of Appeals reversed on the merits. It held that petitioner's drugs were not entitled to an exemption, that an applicant could not withdraw an NDA once it became effective, that the drugs were "covered by an effective application," and that although "me-too" drugs (similar drugs) of other manufacturers would be exempt, petitioner's "me-toos" were not exempt. *Held:*

1. "Any drug" is used in § 107 (c)(4) in the generic sense, which means that the "me-toos" whether the products of the same or of different manufacturers "covered" by an "effective" NDA are not exempt from the efficacy requirement of § 201 (p). Pp. 7–9.

2. Prescription drugs on the market are subject to the 1962 efficacy requirements, for if the 1962 amendments are to be comprehensively meaningful, § 107 (c)(4) cannot be read so as to provide a loophole to permit the marketing of drugs previously subject to new drug regulation without demonstrating by the new statutory standards that they have the claimed efficacy. Pp. 9–10.

3. The congressional purpose was to exempt only those drugs that never had been subject to the drug regulation, and therefore any drug for which an NDA had once been effective does not fall within the exempt category. Pp. 10–11.

461 F. 2d 223, affirmed.

DOUGLAS, J., delivered the opinion of the Court, in which all Members joined, except BRENNAN, J., who took no part in the consideration or decision of the case, and STEWART, J., who took no part in the decision of the case.

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SUPREME COURT OF THE UNITED STATES

No. 72-666

USV Pharmaceutical Corporation, Petitioner,
v.
Caspar W. Weinberger, Secretary of Health, Education, and Welfare, et al.

On Writ of Certiorari to the United States Court of Appeals for the Fourth Circuit.

[June 18, 1973]

MR. JUSTICE DOUGLAS delivered the opinion of the Court.

Petitioner sells a line of drugs containing citrus bioflavonoid as a principal active ingredient which is an extract from fruit skins. The drugs are sold in capsules, syrup, and tablets. In the 1950s NDAs were filed and became effective for seven of them; two, however, were sold without any NDA. In 1961 FDA advised petitioner that two of the products, when distributed under the existing labels, were not new drugs. These drugs were recommended for a wide variety of ailments from bleeding to hypertension to ulcerative colitis. After the 1962 amendments these products, together with a large number of other bioflavonoid products, were examined by FDA for drug effectiveness. NAS–NRC panels reviewed them. One panel on Metabolic Disorders concluded that the "use of these materials as hemostatic agents for capillary fragility is felt to be unjustifiable and not proved." A panel on Hematologic Disorders found there was no proof that these products were efficacious for any medical use.

Based upon the NAS–NRC reports and its own evaluation, FDA gave notice of opportunity for hearing on its

proposal to withdraw approvals of NDAs for all drugs containing these compounds, alone or in combination with other drugs. Petitioner thereupon brought suit in the District Court, asking for a declaratory judgment that its drugs are exempt from the efficacy requirements under § 107 (c)(4). The administrative proceedings went forward, FDA refusing a stay pending the judicial proceedings. Petitioner submitted no evidence of "adequate and well-controlled investigations" as required by § 505 (d) of the Act to support its claims of effectiveness. The Commissioner made findings and withdrew petitioner's NDAs.

In the District Court the petitioner contended that the drugs were exempt from regulation by reason of § 107 (c)(4) of the 1962 amendments which provides:

> "In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201 (p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day."

The District Court found that two of the products had never been covered by effective NDAs and that, while seven had been covered, their applications had later been withdrawn by petitioner. It found that the products were "safe" for use in treating abnormal capillary permeability and fragility. It therefore concluded that, as of the day the 1962 amendments became effective, petitioner's products were not new drugs, were not covered by effective applications within the meaning of § 107 (c)

(4), and hence were exempt from the effectiveness criterion added to the regulatory provisions of §§ 505 and 201 (p). In so ruling, the District Court necessarily determined that it, and not the Food and Drug Administration, had jurisdiction to decide exemption questions. — F. Supp. —.

The Court of Appeals agreed that the District Court alone had jurisdiction and reversed on the merits.[1] 461 F. 2d 223. It held that none of petitioner's bioflavoinoid drugs were entitled to exemption under § 107 (c)(4). As to the seven for which NDAs had been filed, it held that an applicant could not withdraw an NDA once it became effective. It concluded that even if the drugs were generally recognized as safe on the day preceding the effective date of the 1962 Act, they were "covered by an effective application" within the meaning of § 107 (c)(4)(C) and thus were not exempt from the 1962 amendments. As to the "me-too" drugs, those specific drugs for which petitioner had not filed an NDA, the Court of Appeals held that although the "me-toos" of other manufacturers competing with petitioner's bioflavonoids would be exempt, petitioner's "me-toos" were not exempt

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[1] Unlike the situation in *CIBA Corp.* v. *Weinberger*, *ante*, at —, the order of the Commissioner withdrawing petitioner's NDAs had not become final prior to the District Court assuming jurisdiction. In fact, the Court of Appeals for the District of Columbia Circuit reversed the Commissioner's decision, 466 F. 2d 455, and the proceedings on remand are now pending before the Commission. Thus, petitioner was not barred from proceeding in the District Court. Cf. *CIBA Corp.* v. *Weinberger*, *supra*. Our decision today is not meant to indicate that the District Court, had it concluded that its jurisdiction was concurrent with that of FDA, would not have abused its discretion in refusing to stay this action pending the outcome of administrative proceedings. Cf. *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, *ante*, at —. The Court of Appeals below found it unnecessary to consider whether petitioner had failed to exhaust its administrative remedies. 461 F. 2d, at 226.

because the NDAs covering the pioneer drugs prepared by petitioner covered all of its products similar in formula and labeling. While the Government agrees that petitioner's "me-too" products should be accorded the same treatment as the "me-toos" of other manufacturers who had never filed NDAs, the parties are at odds on other issues.[2]

The resolution of the questions presented turns essentially on the meaning of § 107 (c)(4), quoted above. But as background for the problem of construction, references should be made to other 1962 amendments. Section 201 (p) [3] was amended to redefine a "new drug" as one not generally recognized by experts as both safe and effective for use under the conditions prescribed or one that has not been used to a material extent and

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[2] There lurks in the case a question whether a drug could have been unsafe prior to the 1962 amendments because it was ineffective in treating the conditions for which its use was recommended by the label. That question, however, was not presented in the petition for certiorari.

[3] "The term 'new drug' means—

"(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a 'new drug' if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

"(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."

for a material time. Section 505 (a) was amended to require affirmative approval of FDA, where previously it had provided that an NDA would automatically become effective unless a contrary order were issued.[4] Section 505 (d) [5] was amended to require disapproval of an appli-

[4] Section 505 (c) provides:

"Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

"(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

"(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

[5] That section provides:

"If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him

cation if there is "a lack of substantial evidence that the drug will have the effect it purports or is represented to have." Section 505 (e) was amended to require that any previous approval of an application be withdrawn whenever it appears from new information or otherwise that there is a lack of substantial evidence of the drug's effectiveness.

There remained the problem of the application of the new drug efficacy provisions to drugs already on the market. Without transitional protection all drugs—except those marketed prior to the 1938 Act whose labeling had not been changed and which were exempt from the "new drug" provision of § 210 (p)—would have been in violation of the amended Act unless generally recognized as effective. Even NDAs which were outstanding would have become ineffective because FDA had not approved them under the new criteria. Section 107 (c) (2) of the amendments therefore provides that applications which were effective on the day before the enactment date of the 1962 amendments should be deemed

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as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is presented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

"approved." Section 107 (c)(2) thus eliminated the necessity to review and approve every application already on file.

Section 107 (c)(3) provides that drugs covered by NDAs already on file whose labeling remains unchanged are not affected by the amended provisions of § 505 (b) or by approvals or refusals under § 505 (d) insofar as the effectiveness of the drugs is concerned, so long as the application is not withdrawn or suspended under § 505 (e). It also provides that the new effectiveness requirement in the withdrawal provision would not apply until two years after the amendments were adopted, or until the NDA approval were withdrawn for reasons other than lack of the drug's effectiveness, whichever came first. It seems apparent that by reason of § 107 (c)(3) the industry was assured it could continue to market previously approved NDAs unless and until the NDA was withdrawn and that before such withdrawal they would be given a minimum of two years within which to submit "substantial evidence" to support the claims for their products.

Section 107 (c)(4) exempted drugs from the new effectiveness requirements so long as their composition and labeling remained unchanged. This exemption, however, applies only to a product that, on the day before the 1962 amendments became effective, (A) was used or sold commercially in the United States, (B) was generally recognized by the experts as safe; and (C) was not "covered" by an "effective" application.

The first question is, which "me-too" copies of an NDA drug are subject to the efficacy requirements to the same extent as the NDA product itself? Are only the "me-toos" of the same manufacturer "covered" by an effective application within the meaning of § 107 (c)(4)(C) and thus not exempt from § 201 (p) or are no "me-toos" exempt whoever manufactures them? It seems clear

that § 107 (c) was designed in general to make the new 1962 requirements applicable to drugs then on the market after a two-year grace period. Section 107 (c)(4) created an exception from this general policy. Senator Eastland explained these "transitional provisions," stating: [6] "Established drugs which have never been required to go through new drug procedures will not be affected by the new effectiveness test insofar as their existing clauses are concerned." It is true that an NDA covers a particular product or products that it names and that § 505 when applied to an NDA is personal to the manufacturer who files it. Section 505, in other words, addresses itself to drugs as individual products. But we agree with the Government that "any drug" when used in § 107 (c)(4) is used in the generic sense, which means that the "me-toos" whether products of the same or of different manufacturers "covered" by an "effective" NDA are not exempt from the efficacy requirements of § 201 (p). If that were not true, then, as the Court of Appeals said, the "me-toos" of one manufacturer covered by an NDA of another manufacturer would be exempt from regulation, while the "me-toos" of the manufacturer holding the NDA could be regulated. That seems to be a reading of § 107 (c)(4) that is discriminatory and needlessly so. For it is avoided by taking "any drug" in that subsection as a generic term. The transitional nature of § 107 (c) works in that direction. A reading to exclude all "me-too" drugs from the word "covered" as used in § 107 (c)(4) would create an hiatus in the regulatory scheme for which there seems to be no cogent reason. We find no persuasive reason to resolve the ambiguities in favor of the manufacturers so that pre-existing pioneer drugs would be subject to the new efficacy requirements but the "me-toos" which often do equal service for them would escape

[6] 108 Cong. Rec. 17366.

the thrust of the 1962 amendments. That resolution of the ambiguities would largely leave pre-1962 drugs of unproved effectiveness untouched by the 1962 amendments and perpetuate a competitive contest in the marketing of ineffective pre-1962 drugs. FDA would, of course, have authority to pursue that category of drugs under the misbranding provisions of the Act. But that slow cumbersome method is utterly unsuited to the need. We decline to attribute such a self-defeating purpose to the Congress. After all, the 1962 regulatory scheme proposes administrative control through an expert agency in lieu of the more cumbersome 1938 devices, as a result of which, "good medical practice is hampered, and the consumer is misled until, perhaps years later, the Government has gathered the necessary evidence to sustain its burden of proving the violation in court." [7]

Petitioner, focusing on prescription drugs,[8] contends that the construction of § 107 (c)(4) urged by the Government would make the exemption meaningless. Prescription drugs, as FDA points out, are not likely to have come on the market subsequent to 1938 without being a "new drug" for some time. But the OTC drugs, known as the proprietaries, are often made up of old, established ingredients. Such products, coming on the market for the first time between 1938 and 1962, might never have been subject to new drug regulation. If so, they would be entitled to the exemption provided by § 107 (c)(4). Senator Kefauver, the main sponsor of the 1962 Act, deplored the absence in an earlier bill of the

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[7] H. R. Rep. No. 2464, 87th Cong., 2d Sess., at 3.

[8] Prescription drugs, as defined by § 503 (b), 21 U. S. C. § 353 (b), include any drug for human use which (A) is habit-forming; (B) "because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe except under the professional supervision of a practitioner licensed by law to administer such drug"; or (C) is limited to prescription used in the application under § 505.

failure to submit proprietaries on the market to tests of efficacy. He said: [9]

> "Effectiveness, as well as safety, should apply to new proprietary drugs, but proprietaries now on the market are not to be subject under the present bill to the provisions requiring them, upon notice by the FOA (*sic*), to support their claims for effectiveness. I think they should be so required. That is a matter which can be remedied in conference or by other legislation."

It can be inferred from this statement that prescription drugs on the market were to be subjected to the efficacy requirements. If the 1962 amendments are to be comprehensively meaningful, we decline to read § 107 (c) (4) so as to provide a loophole so that the manufacturers can go on marketing drugs previously subject to new drug regulation without demonstrating by the new statutory standards that they are effective as claimed.

The second question presented by this case is whether an applicant could have withdrawn or "deactivated" an NDA prior to the 1962 amendments so that its drug was no longer "covered by an effective application" and thus is now exempt from efficacy regulation by reason of § 107 (c)(4). Petitioner in 1961 had stated in a letter to the Director of New Drug Branch of the Bureau of Medicine in FDA that "[i]t is our recollection that the C. V. P. class of products were no longer considered to be new drugs . . . ." Petitioner in 1961 also stopped filing supplemental information as required by regulation with regard to the products for which NDAs had become effective. It claims that these acts were sufficient to withdraw the NDAs and to bring its products within the exemption.

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[9] 108 Cong. Rec. 17368.

Initially, we repeat that the legislative history indicates that it was Congress' purpose to exempt only those drugs that never had been subject to the new drug regulation.[10] Quite obviously, any drug for which an NDA once had been effective does not fall within that category.

Congress rejected an approach that would have exempted from the efficacy reqirements of the 1962 amendments all drugs then marketed which had become generally recognized as safe. It now would be irrational for us to construe § 107 (c)(4) of the amendments to exempt a drug merely because the manufacturer had taken some formal steps totally unrelated to the drug's effectiveness to indicate that the drug was no longer a "new drug" under the pre-1962 standards. The result would be that some drugs for which an NDA had been filed would be subject to the efficacy requirements and some would not, even though one could not differentiate between the drugs on the grounds of effectiveness. For example, 43 NDAs had been filed with respect to bioflavonoids and related compounds. There is no reason to believe that any product is more or less effective than another. According to the Solicitor General, the "state of activity, inactivity, or withdrawal" of the applications varied from one to the next when the 1962 amendments became effective. It would be totally inconsistent with the statutory scheme and the policy underlying the 1962 amendments, as well as patently unjust, to conclude that some manufacturers could continue to market their bioflavonoid products, but others could not. We cannot attribute such an intention to Congress and, accordingly, cannot agree with petitioner that its NDAs had been withdrawn prior

[10] See S. Rep. No. 1744, 87th Cong., 2d Sess., pt. 2, at 8; H. R. Rep. No. 2464, 87th Cong., 2d Sess., 12; H. R. Rep. No. 2526, 87th Cong., 2d Sess., 22–23; 108 Cong. Rec. 17366.

to 1962 so that its bioflavonoid products were no longer "covered by an effective application."

Affirmed.

MR. JUSTICE BRENNAN took no part in the consideration or decision of this case. MR. JUSTICE STEWART took no part in this decision.

